Protocol B3D-US-B029 (STU00207507) NCT03652272

Development and Evaluation of an Electronic health Record-based Medication Complete Communication (EMC^2) Strategy

We will conduct a 2-arm, multi-site, physician-clustered randomized trial to evaluate the impact and scalability of the Phase I, finalized EMC^2 strategy to promote actual safe medication use.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly on date provided below.

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1. Synopsis

Title of Study:
Development and Evaluation of an Electronic health Record-based Medication Complete Communication (EMC^2) Strategy: A Pragmatic, Physician Randomized Trial

Rationale:
There is a well-documented need for effective interventions that can help patients understand and safely adhere to prescribed medications, particularly those with greater potential for harm if not taken correctly. We will leverage health and consumer technologies with our **EHR-based Medication Complete Communication (EMC^2) Strategy** to: 1) inform patients about medication risks and safe use, 2) promote provider education and counseling about prescribed drugs and 3) monitor patient adherence outside of visits. The EMC^2 Strategy could be feasible, sustainable, and readily available to ambulatory care practices.

Objective(s)/Endpoints:

Objectives	**Endpoints**
Primary • **<u>Test</u> the effectiveness of the EMC^2 Strategy, compared to usual care on improvement in patient knowledge of prescribed medications**	• Medication-specific knowledge measured by demonstrated proper understanding of indication, risks and benefits, and side effects at 3 months.
Secondary • **<u>Test</u> the effectiveness of the EMC^2 Strategy, compared to usual care on improvement in safe use and adherence to prescribed medications**	• Medication adherence measured by fill, time to fill, demonstrated proper use, and the ASK-12. at 3 months
Tertiary/Exploratory • **Evaluate the fidelity of the EMC^2 Strategy**	• Patient report of provider counseling • Patient report of receipt of print Rx information • Completion of EHR portal survey • Clinic follow-up (yes or no) for patients identifying Rx concerns via portal survey

Summary of Pragmatic Study Design:

Study B3D-US-B029 (STU00207507) is a 2-arm, multi-site, physician-randomized pragmatic trial to evaluate the impact and scalability of the Phase I EMC^2 strategy to promote safe medication use and adherence.

Treatment Arms and Duration:

Usual Care. Usual care includes 1) variable provider counseling with limited or variable EHR notifications or counseling support; 2) no distribution of print medication information materials, including FDA Medication Guides in clinics and variable distribution in pharmacies; and 3) limited or no active surveillance of medication use post-visits.

Intervention: EMC^2 Strategy. The final, vetted version of the EMC^2 intervention from Phase I will be imparted. In brief, there are several components to this strategy that will be embedded into the workflow via EHR/patient portal platforms, mostly automating their implementation. Following patient movement through a provider visit, the following activities will occur for a select list of pre-specified medications:

1) Prescribers will receive a 'Best Practices Alert' which recommends patient counseling on medication use and provides an overview of key medication risks
2) Patients will receive a Medication Guide + Summary with their After Visit Summary
3) Patients will be asked to complete a brief questionnaire on medication use via the patient portal post visit (at both 1 week and 1 month post visit for this phase of the study)
4) Portal assessment results and feedback will be provided to the clinic via an inbox message. Clinic staff will respond to any identified problems according to their own clinical care protocols.

Number of Patients:
While our expected sample size for this pragmatic study is 300, we will recruit 330 patients (~200 at NU, ~100 at ACCESS ; we anticipate 90% retention among the recruited sample by 3 months (n=297). We therefore will oversample to accommodate some attrition.

Statistical Analysis:
We will perform analyses to address each of the aims using SAS v9.4 (SAS Institute, Cary, NC). The proposed trial uses a cluster-randomized design where the prescribing physician will be randomized to one of two arms (usual care, EMC^2). Given the brief follow-up period, we anticipate ~90% retention at T2 interview. These estimates result in 330 patients recruited with an anticipated 300 patients (150 per arm, 6 per physician) available for primary data analysis.

> We will use generalized linear mixed models (GLMM) to test treatment effects, specifying identity link for continuous and the logit link for binary outcomes using PROC GLIMMIX in SAS (v.9.4). All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05.

Resources Available:
This study is led by senior health services researchers with expertise in chronic disease management, health literacy, and complex research designs. Additionally, the project staff have worked on similar research projects and have adequate training to carry out the proposed pragmatic study.

Setting:
This study is being conducted with patients from clinics within Northwestern Medical Healthcare (NMHC) and Access Community Health Network (ACCESS). All physicians within the practice will be informed of the study.
All telephone interviews will take place in a private space at all study sites.

2. Schedule of Activities

Table 1 shows study timeline.

Visit						
Days from Initial Index Visit	1-2	3-14	15-21	21-28	29-36	90-104
Pragmatic Study Procedure						
Screening Phone Call	X					
Written Informed consent	X					
T1 In Person* Interview	X	X				
Patient sent email to complete portal questionnaire (expires after 2 weeks)		X		X		
If questionnaire not complete reminder email sent (sent two days after initial email to complete portal questionnaire)			X		X	
T2 Phone Interview						X

*T1 interview may be completed over the phone if an in-person interview cannot be conducted.

3. Introduction

3.1. Pragmatic Study Rationale

Research has repeatedly demonstrated that individuals lack essential information on how to safely take prescribed (Rx) medications(1-4). An Rx communication and adherence strategy may be helpful for prescribers to ensure that patients are adequately informed about the medications they are taking and activated to sustain safe, appropriate use. We are therefore proposing to refine and evaluate our EMC^2 strategy to support safe prescription medication use.

3.2. Background

Inadequate patient knowledge has been cited as a root cause of unintentional misuse and non-adherence, which can lead to suboptimal treatment benefits and/or serious adverse drug events(5, 6). But this should not be surprising, as neither physicians nor pharmacists routinely counsel patients on their medication regimens(5, 7, 8). Instead, patients heavily depend on product labeling, such as package inserts, container labels, leaflets, and Medication Guides and/or Medication Summaries– all of which are limited in their clarity and effectiveness (5, 9, 10). 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 unintentional non-adherence(9).

An Rx communication and adherence strategy may be helpful for prescribers to ensure that patients are adequately informed about the medications they are taking and activated to sustain safe, appropriate use. This is most salient for Rx regimens the Food & Drug Administration (FDA) has deemed to possess serious public health concerns, warranting additional risk minimization activities beyond the product label [including a 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.

A pilot study was recently conducted to assess the feasibility and acceptability of an Electronic health record-based Medication Complete Communication (EMC^2) strategy that leverages electronic health record (EHR) technologies to: 1) prompt and guide provider counseling using 'best practice alerts (BPAs); 2) automate the delivery of Medication Guides and/or plain language Medication Summaries (Medsheets) at prescribing; 3) activate patients post-visit via the patient portal to confirm they have sufficient Rx information and are taking their Rx regimens properly; and 4) engage the clinical team to help patients overcome any barriers to adherence or safety. The results of this pilot were positive; the EMC^2 strategy was successfully implemented at two diverse, academic clinic practices utilizing the EPIC EHR. Findings include:

- ≥80% threshold for success achieved for BPAs, Med Guide/Medsheet delivery;
- While the Portal Survey was able to be consistently sent out to patients, this was most reliable among patients who already had an active Epic MyChart account;
- Results indicate high levels of patient satisfaction with EMC^2 tools and substantially higher rates of provider-patient counseling than reported previously in the scientific literature

Key lessons learned from the pilot were then used to inform this pragmatic trial to evaluate the efficacy of the EMC^2 intervention, specific to its ability to improve counseling rates, patient understanding and safe use of select medications compared to usual care.

3.3. Benefit/Risk Assessment

Risk to Patients:

Participation in the study poses minimal risk of psychological, social or economic harm. Informing patients 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 patients in this study.

Potential Benefits to Patients:

It is possible that patients enrolled in the intervention study arms may directly benefit in that they may have, as a result of this study, a better functional understanding of their medication. The results of this study may provide

important information regarding how strategies can be implemented via the EHR and computer technologies to support safe and appropriate medication use.

Provisions to Protect the Privacy Interests of Patients:
In order to preserve patients' confidentiality rights, research patients will be assigned code numbers that will be used to identify all the information collected. Using these codes, none of the collection forms will contain the names of the patients. All electronic data will be stored on a password-protected computer. A master study tracking database via Microsoft Access, at Northwestern, will contain information linking patients to their study identification numbers. This database will be encrypted and password protected and/or, kept on a secure server, and only accessible by Northwestern study personnel. ACCESS participants will be additionally tracked in their EPIC EMR system, only accessible by ACCESS study personnel. Survey data will be stored in a REDCap. The data will not contain any identifiable information. Individual study identification numbers will be assigned to each patient and only this number will appear on the survey.

All enrolled patients will provide written consent, include HIPAA authorization, for the collection of all data. Only authorized personnel listed on the IRB and approved by the PI will have access to the data.

4. Objectives and Endpoints

Table 2 shows the objectives and endpoints of the pragmatic study.

Table.2.

Objectives	**Endpoints**
Primary • **Test the effectiveness of the EMC^2 Strategy, compared to usual care on improvement in patient knowledge of prescribed medications**	• Medication-specific knowledge measured by demonstrated proper understanding of indication, risks and benefits, and side effects at 3 months.
Secondary • **Test the effectiveness of the EMC^2 Strategy, compared to usual care on improvement in safe use and adherence to prescribed medications**	• Medication adherence measured by fill, time to fill, demonstrated proper use, and the ASK-12. at 3 months
Tertiary/Exploratory • **Evaluate the fidelity of the EMC^2 Strategy**	• Patient report of provider counseling • Patient report of receipt of print Rx information • Completion of EHR portal survey • Clinic follow-up (yes or no) for patients identifying Rx concerns via portal survey

Abbreviations: **EMC^2-** Electronic health Record-based Medication Complete Communication

5. Pragmatic Study Design

5.1. Overall Design

For Phase II, we will conduct a 2-arm, multi-site, physician-randomized pragmatic trial to evaluate the impact and scalability of a refined version of the Phase I, finalized EMC^2 strategy to promote actual safe medication use. There will be two study arms: the EMC^2 Strategy, as refined from findings in Phase I, or usual care. Prescribers will be randomized to study arm prior to the initiation of the study. As patients are enrolled in the study, they will be assigned to either intervention or usual care arms based upon the assignment of their physician (see 7.3 Method of Treatment Assignment). We will follow patients for up to three months after receiving a new prescription or a dose change (refills allowed at ACCESS sites only) to determine whether those receiving the EMC^2 Strategy are more knowledgeable, more likely to be safely using their medication, and more adherent (as measured by fill (yes or no), time to fill (days from prescription order to pharmacy pick-up), self-reported behavior, and demonstrated use). We have powered this study as a randomized trial to detect meaningful effects of our intervention. As such, findings will support the more widespread EMC^2 adoption and dissemination.

Multi-Site Research:
The performance sites include Northwestern University, Northwestern Medical Group, and Access Community Health Network. All sites will be involved in the development of EHR tools. Northwestern University will be the data management site and Northwestern RAs will conduct all data collection.

All required approvals will be obtained at each site prior to project implementation. In addition:

a. Once IRB approval is obtained at Northwestern University for study materials and protocol, Access Community Health Network will be sent approved materials via email. Northwestern will send any modifications made to be approved prior to implementation. All study sites will have regular conference telephone calls during both phases of the study to discuss any problems and interim results, and to discuss any possible changes that need to be made to study materials and protocol.

b. All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Study-Wide Recruitment Methods:
Patient Recruitment Process:
At all study sites, a research coordinator (RC) will log in to EPIC to look for an alert if a patient received a new prescription or a dose change for one of the study medications at the study clinic. However, we anticipate that mostly patients with a new prescription will be recruited due to the design of the intervention within EPIC. Alerts in EPIC will only be activated for patients that have not opted out of research. RC will then review the EHR to confirm new or changed prescription and patient portal status. Recruitment will be done by the RC via telephone. Patients will be called via telephone within 1-14 days after their index clinic visit. If they are interested in participating or learning more about the study, the RC will obtain verbal permission to ask the patient a brief series of questions to determine eligibility. If eligible, the RC will schedule a time to complete the T1 interview in person and obtain written consent. If an in person interview is not able to be completed due to COVID-19 institutional policy, the RC will schedule a time to complete the T1 interview over the phone. If all T1 questions cannot be completed in person, they will be completed over the phone.

Table 3 shows patient payment.

Patient Payment:

Research Interview	Payment	Form of Payment
T1	$ 30	Cash at close of interview for in person interview OR Money Order or PNC Visa gift card for telephone interview

T2	$ 40	Money order or PNC Visa Gift Card sent at close of interview

Research Coordinator Training. The project lead will lead sessions to orient the research staff to the surveys and study protocols (e.g., interview process, use of laptop PCs, data security). All interviewers will be required to demonstrate competence in survey administration. All RCs have completed human subjects training (CITI) and intensive training from Drs. Wolf and Bailey in interview protocols and safe data transfer.

Clinic Orientation. Within 1-2 weeks to the launch of the EMC^2 Strategy at the clinic, Drs. Wolf, Bailey, and/or Dr. Wallia for Northwestern OR Danielle Lazar for ACCESS Community Health Network will describe the study and what to expect over the upcoming several months to clinic providers and staff. Additional meetings may be held with staff responsible for following up with patients. We anticipate little orientation will be needed as most these sites participated in Phase I.

Study Timelines:
An individual patient will be involved in the study for a total of up to 3 months. They will complete a screener enrollment interview, a T1 in person or phone interview as soon as possible following the screener, and a final T2 interview on the phone at 3 months.

We anticipate that patient enrollment will actively take place until Q2, 2020.

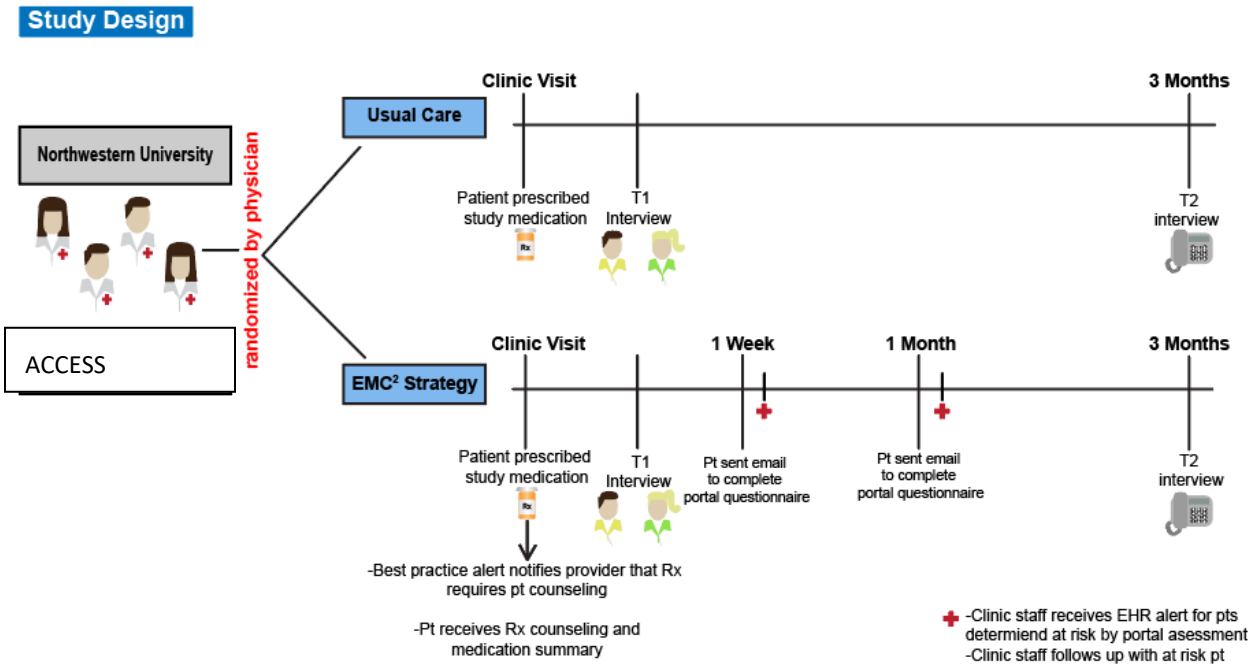
Our proposed/anticipated study timeline is below.

Table 4 shows study measures and outcomes.

Study Measures and Outcomes

		Clinic Visit- BPA, Rx counseling, and Med Summary	Interview	Portal Questionnaire- 1 Week	Portal Questionnaire- 1 month		
Variable	**Instrument(s) or Measure(s)**		**T1**			**T2**	**EHR Review**
Covariates							
Socio-demographics	Age, sex, race/ethnicity, education, income, insurance/work status, living situation		•				
Baseline Health Status	Self-reported overall health/chronic conditions		•				
Health Literacy	Chew		•				
Social Support	Tangible social support scale, marital status		•				
Patient Activation	Consumer Health Activation Index (CHAI)		•				
Effectiveness Outcomes							
Medication Knowledge	Dosage, storage, indication, risks and benefits, side-effects		•			•	
Medication Adherence	Self report fill and time to fill		•			•	
	Proper use		•			•	
	ASK-12		•			•	
Fidelity Outcomes							
Provider Counseling	Receipt of provider counseling (yes/no)		•				
Qualify of Provider Counseling	CAHPS- communication about medicines		•				
Receipt of Materials	Receipt of Med Guide (yes/no)		•				
Perceived Helpfulness	How helpful was intervention? (1 to 10 scale)		•				
Pharmacy Counseling	Receipt of pharmacy counseling (yes/no)		•			•*	
Qualify of Pharmacy Counseling	CAHPS- communication about medicines		•			•*	
Receipt of Portal Email	Completion of portal assessment (yes/no)					•	
	How helpful was intervention? (1 to 10 scale)					•	
Clinic Staff Follow-Up Counseling	Receipt of counseling (yes/no)					•	
Quality of Clinic Staff Counseling	Self-reported clinic follow-up					•	
Frequency of Clinic Follow-Up	EHR Review of clinic contact with patient						•
***only if not filled at T1**							

Figure.1 Illustrates the study design



5.2. Number of Patients

Patients will be screened to achieve 300 randomized and 300 evaluable patients for an estimated total of 150 evaluable patients per treatment group. Approximately 10 providers will recruited for study feedback. To address potential retention loss (estimate 90% retention), we will target 330 patients to be recruited and consented to the study, completing the baseline assessment.

5.3. End of Study Definition

The end of the study will be when the last visit by the last study patient is completed.

5.4. Scientific Rationale for Pragmatic Study Design

Control is usual care, as that is what patients currently receive. We are doing a physician randomization instead of patient randomization because of the potential for contamination (the intervention is diffuse) and the inability to pre-randomize patients before their clinic visit.

5.5. Justification for Dose

Not applicable.

6. Study Population

Patients will be screened for eligibility via telephone within 7 days of patient's clinic visit.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening/enrollment:

All patients. regardless of study arm, must meet the following eligibility criteria:

1) Patient is age 18 and older
2) Patient is English speaking
3) Patient is primarily responsible for administering their own medication
4) Patient must have received a new or changed prescription for a product(s), identified by Eli Lilly and the study team, within 7 days of recruitment*
5) Patient must have access to the internet
6) Patient must have a patient portal account

*Eligibility criteria may include refills for study medications at ACCESS sites only for the following reasons:

1) We have learned 60% of the BPAS are considered ineligible at ACCESS primarily due to refills. To meet BPA volume and milestone goals, Lilly USA and the study team will expand eligibility critiera for refills at these sites only.
2) ACCESS patients do not have the appropriate equipment to at home to monitor health status (for ex. glucose monitor) thus the majority of patients are seeing their doctors to only refill medicines during the COVID-19 pandemic.

Providers must meet the following eligibility criteria:

1) Provider working at a study site during study dates.

Type of Patient and Disease Characteristics

We will be recruiting patients who have been prescribed at least one of our target medications.

Informed Consent

Patients must be able and willing to give written informed consent.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening/enrollment:

1) Severe, uncorrectable vision

2) Severe hearing impairments

3) Severe cognitive impairment

4) No access to the internet or patient portal account

Adults unable to consent, individuals under the age of 18, and prisoners will be excluded from this research.

For many patient characteristics, we will be able to ascertain differences between those participating and those who refuse to be included in the study, to determine potential bias. Additionally, research teams at both sites will limit recruitment of patients prescribed Metformin to 50 patients per site and will only recruit those with a new prescription. This quota has been set in place to ensure adequate representation of other study drugs with less volume compared to Metformin.

6.2.1. Medical Conditions

Not applicable.

6.2.2. Lifestyle Restrictions

Not applicable.

6.3. Screen Failures

Eligibility screening will take place before the written informed consent. Verbal consent will be obtained to ask screening questions. Individuals who do not meet the criteria for participation in the study (screen failure) may be rescreened and invited to participate a second time if they are prescribed a study medication at a different time. Intervals will vary and will depend on the date on which the medication was prescribed.

7. Treatments

7.1. Treatments Administered

This pragmatic study involves a comparison of intervention administered with standard of care in routine care.

Study Arms.
Usual Care: For this study, current usual care includes 1) variable provider counseling without any EHR notifications or counseling support; 2) variable distribution of print medication information materials, including FDA Medication Guides in clinics and variable distribution in pharmacies; and 3) limited or variable active surveillance of medication use post-visits.

Intervention: EMC^2 Strategy: There are several components that will be embedded into the workflow via EHR/patient portal platforms, mostly automating their implementation. Following patient movement through a provider visit, the following 6 activities will occur:

1. *Physician Medication Alert:* If a prescribing physician attempts to place a new order or change to an existing study medication prescription, an EHR-generated alert will notify the provider that the medication requires patient counseling. Physicians can opt to ignore this alert.

2. *Provider Counseling Support:* Content from the 1-page, Med Guide Summary will appear on the screen, if selected by the provider, to orient and inform provider-patient discussion.

3. *Automated Delivery of Med Guide + Summary:* When patients leave an encounter, the medication order in Epic will automatically cue printing of both the 1-page, health literate Med Guide Summary for study medications and a full Med Guide, if applicable (latter is required by FDA for certain medications only, the former designed to enhance comprehension). If the medication was ordered during a telemedicine encounter, the Med Guide Summary will automatically populate in the patient portal.

4. *Follow-Up Portal Questionnaire:* Within 1 week post-visit, patients will receive an automated email prompting them to log on to the patient portal. Patients' will be asked to fill out a short set of questions related to medication adherence, and other medication-related concerns (i.e. cost, side effects). If patients have not completed the questionnaire within 2 days, another email reminder will be sent. The information submitted back by the patient will be stored in the EHR.

   Content in question form and corresponding responses for the portal questionnaire will be revised from prior evaluation scripts and written by Drs. Wolf, Bailey, Chung, and Wallia.

   The addition of the patient portal will provide opportunities to have ongoing communications with their clinic, access to regimen-specific medication information, and to provide a feedback loop informing healthcare providers of safety and adherence-related behaviors and concerns.

5. *EHR Inbox Message to Clinic*: The results of the patient portal questionnaire will be sent back to the EHR, populating an inbox message notifying the nurse/clinic staff and/or physician if a patient has a medication risk alert, detailing the nature of the issue (i.e. education needed, adherence problem, side effect concerns, etc.). The system will be flexible and allow the clinic to specify actions to be taken according to their workflow preferences; the default plan is that patient contact will be undertaken by nurses/clinic staff involved with care management.

6. *Clinic Counseling:* If a problem/concern is flagged during the review of the portal questionnaire, there will be an expectation for a clinic staff member to respond to the concern by calling the patient. A general orientation to staff at the clinic will provide guidance on how to perform brief counseling based on each specific clinic protocol.

7.2. *Treatment Regimens*

Not applicable.

7.2.1. Packaging and Labelling

Not applicable.

7.2.2. Medical Devices

Not applicable.

7.3. Method of Treatment Assignment

As the EMC^2 Strategy includes changes to healthcare delivery, the intervention itself is diffuse and individual patient randomization is not feasible. Therefore, randomization will occur at the provider (specifically, prescriber) level (N= ~50 eligible clinicians). Specifically, prescribers will be randomized to study arm (EMC^2 Strategy or usual care) prior to the initiation of the study. As patients are enrolled in the study, they will be automatically assigned to either intervention or usual care arms based upon the initial assignment of their physician. This specific strategy of "turning on" an EHR intervention with physician 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]. To optimize the likelihood of obtaining similar populations in each study arm, physicians will be placed into 4 strata based on workload (full time vs. part time) and site and randomly assigned to one of the two arms with an equal number assigned to each arm within each strata.

7.3.1. Selection and Timing of Doses

Not applicable.

7.4. Blinding

This is an open-label pragmatic study. As with most behavioral interventions, it will not be possible to fully blind researchers, healthcare providers, and study patients to intervention vs. usual care assignments. However, we have purposefully designed our trial to prevent certain threats to contamination between study arms. Patients will be told they will receive one of two models of care. While they will not be deliberately made aware of the approach not received, we do recognize that there is an unavoidable risk of patients learning from other patients involved in the study.

7.5. Dosage Modification

Not applicable.

7.6. Preparation/Handling/Storage/Accountability

Not applicable.

7.7. Treatment Compliance

Patient compliance with intervention will be assessed at end of intervention course. Compliance will be assessed during patient interviews.

7.8. Concomitant Therapy

Not applicable.

7.9. Treatment after the End of the Study

7.9.1. Study Extensions [if applicable]

Not applicable.

7.9.2. Continued Access

Not applicable.

7.9.3.Special Treatment Considerations [if applicable]

Not applicable.

7.9.4. Patient Follow-Up in Pragmatic Trials [if applicable]

The T2 interview will take place over the phone 3 months after T1. Patients in the EMC^2 strategy group will also receive portal questionnaires.

8. Discontinuation Criteria

8.1. Discontinuation from Pragmatic Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

There are no anticipated circumstances when a patient would be withdrawn from the study without their consent, unless they pose a threat to themselves or research staff.

Patients can choose to withdraw from the study at any time. If a patient 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.

8.1.2. Temporary Discontinuation from Study Treatment

Not applicable.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor and the investigator to determine if the patient may continue in the study. If both agree it is appropriate to continue, documented approval from the sponsor will be obtained to allow the inadvertently enrolled patient to continue in the study.

Some possible reasons that may lead to permanent discontinuation include:

- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
    - the investigator decides that the patient should be discontinued from the study
- patient decision
    - the patient or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study

8.2. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Pragmatic Study Assessments and Procedures

Please see section 5 for the Schedule of Activities, with the study procedures and their timing.

9.1. Effectiveness Assessments

9.1.1. Primary Effectiveness Assessments

Medication Knowledge. Medication-specific knowledge measures will be created to determine whether a patient has a basic understanding of their prescribed medication. This will comprise a set of objective, open-ended, yet targeted questions with predetermined correct responses known for each medication under study. Patients will be asked about their medication's 1) indication, 2) risks or warnings (knowledge of at risk/warnings, correct or incorrect per warning), and 3) side effects (knowledge of at least two side effects, correct or incorrect per item). Correct answers will be tailored to the available content included in the MedGuide Summary, as done previously by our team.(11-14) While patients are not given response options to facilitate their answer, interviewers will both document the verbatim response to each question and code it as correct or incorrect. A second, independent reviewer, blinded to the research interviewer's code of correct/incorrect, will rate the responses. Any discordance will be resolved through team discussions. Total scores will range from 0-100, calculated reflecting the percent correct of possible points.

9.1.2. Secondary Effectiveness Assessments

Medication Adherence. Medication adherence refers to a patient's medication taking behavior in terms of the extent to which he or she takes the medication as prescribed. We will assess medication adherence by 1) treatment initiation (yes or no), 2) time to fill (# of days from prescription order to patient fill), 3) subjective self-report of medication adherence behaviors (ASK-12), 4) objective assessment of proper use.

1) *Treatment initiation*. Patients will be asked whether they have filled their study prescription (yes or no), and whether they intend to fill it.
2) *Time to fill*. We will calculate the number of days between the date the medication was ordered and when the medication was actually filled, based on the patient's self-report of the date of fill stated on the medication's prescription label from the pharmacy.
3) *ASK-12*. The ASK-12 survey is a widely used and previously validated psychometric measure of adherence that covers three domains: inconvenience/forgetfulness, treatment beliefs and behavior(15). In a study among 112 adults with asthma, type II diabetes or congestive heart failure, the tool demonstrated good internal consistency reliability (Cronbach's α 0.75) and test-retest reliability (intraclass correlation 0.79); convergent validity was also demonstrated through correlations with multiple other measures (16, 17) and pharmacy claims data (15). Ask-12 scores range from 12-60, with higher scores translating to greater barriers to adherence.
4) *Proper use.* For the study medication, patients will be asked on what day they last took the medication. While most medications will be daily and the correct response would be 'yesterday' or 'today', some prescribed drugs of interest may be taken weekly or in another manner as directed by their physician. Patients will then be asked 1) How many times during the day did you take it? 2) At what hour/s of the day did you take this medicine? and 3) How much of this medicine did you take each time? A patient's proper timing (last day and # of times per day), dosing (number of pills per dose), and spacing between doses (for BID, TID medications only) will be coded as correct or incorrect. Patients will be classified as having properly used their medication if they correctly reported all components.

9.1.3. Appropriateness of Assessments

There is no universally accepted measure of medication adherence, but following recommendations in the scientific literature, we will measure adherence using multiple assessments that seek to capture various facets of medication use as described in section 9.1.1. These self-report measures are appropriate given the study design. Since one or two interviews will be conducted via phone, we would be unable to use assessments that require in-person administration or orientation (i.e. MeMS caps; pill counts). As

patients are enrolled in the study for three months, pharmacy fill data would also not provide a meaningful measure of adherence (beyond initial fill). Finally, as many of the medications targeted in this study are injectables, conducting a pill count would be unsuitable.

9.2. Adverse Events

Adverse Drug Events (ADE) will be assessed using a questionnaire administered by the RA during the 3 month follow-up phone call. If the patient states that they have experienced an ADE and provides any details, the RA will fill out an adverse event form to send to Eli Lilly. Dr. Wallia at Northwestern (or another clinic contact in the event of her absence) or the Access Community Health Network clinical liaison will also be informed if the patient answers as described above and/or reports they have not contacted their doctor. They will use clinical expertise to determine appropriate next steps. This protocol will comply with our requirements that investigators and other study personnel are requested to report any suspected adverse reactions with any drug to the appropriate party (for example, regulators or the marketing authorization holder) as they would in normal practice as required by applicable laws, regulations, and practices.

9.2.1. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study patients, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational intervention so that the situation can be assessed.

9.3. Treatment of Overdose

Not applicable.

9.4. Safety

Not applicable.

9.4.1. Electrocardiograms

Not applicable.

9.4.2. Vital Signs

Not applicable.

9.4.3. Laboratory Tests

Not applicable.

9.4.4. Other Tests

Not applicable.

9.4.5. Safety Monitoring

Not applicable.

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics OR Genetics

Not applicable.

9.7.1. [Whole Blood and/or Saliva] Sample[s] for Pharmacogenetic Research

Not applicable.

9.8. Biomarkers and specify other analyses

Not applicable.

9.8.1. Samples for Immunogenicity Research

Not applicable.

9.9. Health Economics [OR] Medical Resource Utilization and Health Economics

Health Economics and Medical Resource Utilization parameters were not evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

The sample size for this pragmatic study was based on comparisons of the primary outcome of medication knowledge between the two arms (i.e., usual care vs EMC^2) at the T2 interview. We expect patients in the usual care arm to score an average of 55.6% correct responses (SD=28.4) based on a previous study that tested comprehension of the FDA standard Med Guides to those to be used in this study(9). Enrolling 330 patients and estimating 90% retention at the T2 interview (N=300, 150 per arm, 6 per provider), we will have 80% power to detect a minimum difference of 9.4% between the EMC^2 and the usual care arm assuming a Type I error of 5% (improving from 55.6% to 65.0% or greater). An intra-class correlation coefficient (ICC) of 0.001 was used; we expect clustering of physicians to have minimal influence on outcomes. However, even if the ICC were higher (i.e. 0.01) we could still detect a difference as small as 9.6%.

With the sample size set by the primary outcome, we also report minimum detectable differences for medication adherence measures. We estimate 65% of the usual care arm to demonstrate proper use of their medications based on prior studies(1, 18). With similar assumptions described above, a sample of 300 participants would enable us to detect a minimum absolute difference of 14.4% between arms with an ICC of 0.001 and 14.7% with an ICC of 0.01. We expect participants in the usual care arm to score an average of 27.5 (SD=7.2) on the ASK-12 based on validation studies(15). Retaining 300 participants (150 per arm, 6 per provider) at the T2 follow-up interview we will have 80% power to detect a minimum difference of 2.4 between the EMC^2 and the usual care arm (improving from 27.5 to 25.1 or less) using an ICC of 0.001 and a difference of 2.5 (improving from 27.5 to 25.0 or less) and with an ICC of 0.10. While no cut-off indicating non-adherence is provided, the goal would be for patients to score below 22.5, the average score in patients who took medications exactly as directed in the ASK-12 validation studies(15). We could detect differences smaller than this with the proposed sample size. In addition, differences in subscale scores of 1.3 for behavior, 0.9 for health beliefs, and 1.0 for inconvenience/forgetfulness could be detected between arms assuming mean scores of 10.5 (SD=3.8), 8.1 (SD=2.7), and 8.9 (SD=3.0), respectively, in the usual care arm.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined in table 5.

Table 5 shows study population.

Population	Description
Enrolled	All patients who provide written consent
Randomized	Since this is a provider-randomized study, patients who are enrolled are automatically randomized.
Evaluable	Patients who had no post randomization efficacy measure for the parameter being analyzed will be excluded. Patients will be included in the treatment group they were randomized to regardless of whether the treatment is received as planned.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

We will perform analyses to address each of the aims using SAS v9.4 (Cary, NC).

The proposed trial uses a cluster-randomized design where the prescribing physician is the unit of randomization. We will randomize providers (i.e. attendings and fellows) to one of two intervention arms (usual care, EMC2). To optimize the likelihood of obtaining similar populations in each, providers will be placed into strata based on their

roles (attending, fellow) and historical volume of study medications dispensed (high, medium, low) for attendings. Providers from each strata will be randomized and identities will be revealed after randomization is complete. Patients enrolling in the study are assigned to the study arm of the provider signing their prescription within the EHR.

Given the brief follow-up period, we anticipate ~90% retention at T2 interview. These estimates result in 330 patients recruited with an anticipated 300 patients (150 per arm) available for primary data analysis.

Effectiveness analyses will be conducted on the full analysis set. This set includes all data from all randomized patients completing the outcomes of interest according to the treatment the patients were assigned.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

A detailed description of patient disposition will be provided at the end of the study.

10.3.2.2. Patient Characteristics

T1 assessment will include socio-demographics, social support, and health status, including number of comorbidities. 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.
Health Literacy. We will assess health literacy via the Newest Vital sign or three validated screening questions that assess health literacy skills.
Patient Motivation. The Consumer Health Activation Index (CHAI) assesses patients' 'activation' or motivation to participate in healthcare decisions and actions.

T1 patient characteristics will be compared by arm using t-tests and $\chi 2$ tests, as appropriate. Any significant differences ($p < .05$) across study arms will be entered as covariates in models described below.

10.3.2.3. Concomitant Therapy

Not applicable.

10.3.2.4. Treatment Compliance

Not applicable.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

Aim 1. Test the effectiveness of the EMC^2 Strategy, compared to usual care, to improve patient understanding and safe use of prescribed medications

Medication knowledge is the primary outcome of interest, and will be analyzed as a score ranging from 0-100 reflecting the percent of items correct for each medication. Associations between medication knowledge and potential confounders at the patient (socio-demographic characteristics, comorbidities, # and type of medications taken, new or changed prescription, 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 account for the correlated nature of the data from patients prescribed medications from the same providers, specifying the identity link for the outcome of medication knowledge using PROC GLIMMIX in SAS (v.9.4). Treatment assignment will be the independent variable of primary interest and modeled as a fixed effect, and prescriber will be modeled as a random effect. 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 prescribers.

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 imputation methods and present results as secondary analyses.

10.3.3.2. Secondary Analyses

Aim 2. Test the effectiveness of the EMC^2 Strategy, compared to usual care, to improve patient adherence to prescribed medications

We will repeat all GLMM analyses described in Aim 1, but with medication adherence outcomes relevant to Aim 2. We will specify the logit link for binary outcomes (whether treatment was initiated (yes or no) and proper use (correct or incorrect)) and the identity link for continuous outcomes (time to fill and ASK-12 scores). We will collect data from the EHR related to the study medications (order dates, sig, quantity, type of fill, prescribing provider, etc…) needed to conduct the analyses.

10.3.3.3. Tertiary/Exploratory Analyses

Aim 3. Evaluate the fidelity of the EMC^2 Strategy to promote provider counseling, deliver patient Rx information, and inform providers of potential harms.

Compared to usual care, patients receiving the EMC^2 strategy will:

1) report higher rates and quality of provider Rx counseling

2) report higher rates of receipt of print Rx information

Appropriate bivariate analyses will be performed based on each outcome measure described below using t-tests, Wilcoxon Rank-Sum, or $\chi 2$ tests, as appropriate.

Provider Rx Counseling. We will ask patients (yes/no) whether their provider(s) (physician/nurse) counseled them on their prescribed medication. We will also ask adapted questions from the Health Literacy supplemental items of the Consumer Assessment of Health Providers Survey (CAHPS) to evaluate the extent and quality of physician verbal counseling.

Receipt of print Rx information. All patients will be asked whether they received any print Rx information at their appointment. We will further probe intervention patients to determine whether the health literate Med Guide Summary was specifically received and its perceived helpfulness. Additionally, we will also collect EHR data to determine whether the Med Guide Summary was printed with their after-visit summaries.

We will also examine completion rates of:

1) the EHR portal survey by patients in the intervention arm
2) clinic follow-up for patients identifying Rx concerns in the portal survey.

Completion of the EHR Portal Survey. Intervention patients will be asked (yes/no) whether they received the emails to visit the portal and if they completed the portal questionnaire. We will also confirm this by determining if portal questionnaire results were populated in the EHR.

Clinic follow-up for patients identifying Rx concerns. At each performance site, clinical liaisons will share with the study team what specific medication-related concerns that are self-reported by patients via the portal assessment might warrant follow-up. It is at the discretion of each clinical practice to choose how they will triage the information provided via the feedback from the EMC2 intervention, and as part of the study we will explore the frequency and nature of follow-up that occurred for various medication-related concerns by self-report and in the EHR.

10.3.4. Safety Analyses
Not applicable.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses
Not applicable.

10.3.6. Other Analyses
Not applicable.

10.3.6.1. Health Economics
Not applicable.

10.3.6.2. Subgroup Analyses
Not applicable.

10.3.7. Interim Analyses
No interim analyses are planned for this pragmatic study as risks are minimal and even small effects on adherence rates may be important given the scalability and low cost to implement these interventions. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

11. Appendices

Attachment 1. Abbreviations and Definitions

Term	Definition
AE	Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
EMC²	Electronic health record-based Medication Complete Communication
EHR	Electronic health record
ASK-12	Adherence barrier survey
Rx	Prescribed
CHAI	Consumer health activation index
REMS	Risk evaluation and mitigation strategy
GLMM	Generalized linear mixed model
MAR	Missing at random
CAGOS	Consumer assessment of health providers survey

Attachment 2. Clinical Laboratory Tests

Not applicable.

Attachment 3. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

Patients. Subjects will be informed about the nature of the pragmatic study by a CITI certified RA and asked to provide written informed consent in a private space. Additionally they will be notified that only those contents of their medical record that are necessary to evaluate of the intervention will be released to the research team at Northwestern and ACCESS. Finally, they will be informed about the follow-up telephone interview for the study (3 months post baseline). They will be informed that they may withdraw from the study at any time and given contact information for the PI and study coordinator. These consent forms will be locked in a file cabinet only accessible to necessary research staff. Participants will be given the option to receive a blank consent form for reference if they request it.

Subjects may provide electronic or verbal consent, documented in REDCap, if they cannot complete an in-person interview due to COVID-19 institutional policy. Participants will be asked to complete an online consent with HIPPA authorization and complete the baseline interview by phone after the consent is obtained. The RC will send patients a link to REDCap by email or text message to be able to read through the consent. If the participant agress to participate, they will be asked to electronically sign and date the online consent.

Participants that indicate they do not have the means to e-consent (ie. no access to internet) will be allowed to give verbal consent. In this event, we request a waiver of documention of informed consent and an alteration to obtain verbal HIPPA authorization. Due to institutional restrictions on in-person research activities at participating recruitment sites, research cannot practicably be conducted without this waiver or alteration. Once verbal consent and HIPPA authorization is obtained, the consent date and the name of the RC that obtained the consent will be recorded in REDCap.

All forms of consent will be obtained in a process fashion. During the review of the IRB approved consent document, the subject will be asked to explain in his/her own words of his/her understanding of the consent. This will enable the research personnel to enter into a dialogue with the subject and ensure that the subject understands he/she is free to withdraw at any time without penalty. Additionally, subjects will be encouraged to ask questions prior to giving consent, and all questions/answers will be documented in REDCap. There will be no exertion of any overt or covert coercion. Patients who verbally consent will be emailed or mailed a blank copy of the consent document for their records.

Providers**.** At Northwestern and ACCESS, we will ask providers to consent to be part of the study, which includes consenting to be randomized to one of the two study arms. We are asking for provider consent to allow any providers who are uncomfortable with the study to opt out. As noted in recruitment, providers will be informed of the nature and details of the study via email and a brief overview at a monthly business meeting. Providers will be asked to sign a written consent electronically or in-person to be a part of the study, which includes their consent to allow their patients to be randomized. All providers will be told that their participation is voluntary; they can stop at any time, and whether they participated or not will not be disclosed to their superiors. Their participation in the study will be kept confidential and made anonymous in reports. If the provider does not want to participate or decides to stop before completing the patient enrollment period, this will not be disclosed to any superiors. At the secondary site, providers will be informed of the nature of the study and the details of the study via email and will be told that they may opt out of participating. Any providers who choose to opt out will be removed from the study.

Waiver of HIPAA Authorization are requested to identify subjects (patients) prior to enrollment into the study.

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study

- that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient willingness to continue his or her participation in the trial.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

Appendix 3.1.2. Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- Study protocol and updates during the course of the study
- informed consent form
- relevant curricula vitae

Appendix 3.1.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 3.1.4. Investigator Information

Michael S. Wolf, PhD MPH
Professor, Medicine and Learning Sciences
Northwestern University
750 N. Lake Shore Drive, 10th Floor
Chicago, IL 60611
Phone: (312) 503-5592

Stacy Cooper Bailey, PhD MPH
Associate Professor of Medicine
Northwestern University
750 N. Lake Shore Drive, 10th Floor
Chicago, IL 60611
Phone: (312)503-5595

Appendix 3.1.5. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.6. Final Report Signature

The investigator will sign the final clinical study report (CSR) for this study, indicating agreement with the analyses, results, and conclusions of the report.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Training at the Northwestern and ACCESS will begin after surveys and interview protocols have been refined and standardized. The training will include tailored discussion of 1) roles and responsibilities; 2) HIPAA and IRB mandates (completion of Human Subjects Training Program - CITI; 3) effective recruitment communication and interviewing with attention paid to health literacy and culture; and 4) gathering and recording data including administering the structured survey electronically. Role playing will be used to fine tune training for obtaining informed consent and interviewing patients. Institutional Review Board (IRB) approval will be attained at both sites prior to any active recruitment efforts. All interviewers will be required to demonstrate competence in survey administration

Appendix 3.2.1. Data Capture System

Confidentiality and Data Management:

Data collected includes patient and clinic staff consents, patient and clinic staff interview and/or online survey data. Only authorized personnel listed on each institutions IRB will have access to the data. Any information that could allow identification of individual patients, including the master list, will be kept strictly confidential.

Data Access. The Data Custodian is the Principal Investigator, Dr. Michael Wolf. Only authorized personnel listed on each institutions IRB will have access to the data. Any information that could allow identification of individual participants, including the master list, will be kept strictly confidential.

Local Data Storage. Patient survey data will be stored in REDCap, a secure, web-based application, and on the Northwestern secure server for the length of the study. The Project Lead or Data Analyst will download the data for both sites from REDCap periodically and save to the "Analytic" folder within the Eli Lilly EMC2 project folder on the FSM department servers which are located in a HIPAA compliant data center. These data files do not contain any identifiable information, and are identified by project staff by an assigned study ID. All identifiable information

will remain in a separate database on the secure local servers at Northwestern. ACCESS participants will additionally be tracked in ACCESS's EPIC EMR system and only accessible by ACCESS study personnel. 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. All identifiable information will be deleted upon completion of the study.

Data Monitoring Plan to Ensure the Safety of Participants. This study is low risk and does not require a DSMB. We are testing a simple, EHR-based intervention that will help promote medication safety and help provide an additional mechanism for patients to reach out to their providers if they have any medication-related problems. If an individual patient reports a medication-related problem to research staff, we will advise them to speak to their providers or call 911. As research staff, we will not be directly involved in their medical care or offer medical advice. We will also include language in the consent and in the online portal questionnaire that advises patients to speak to their provider or call 911 if they experience any problems with any medications they have been prescribed.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Attachment 1. References

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Attachment 2. Example Patient Portal Medication Questionnaire

We would like to ask you a few questions about your *[medication name]*.

Please answer each question as best as you can. We appreciate your honesty.

1. During the past week, did you have any of this medicine available for you to take?

   Yes *1*

   No *0*

   If no, please go to the end of the survey and click on the submit button.

2. During the past week, did you decide to stop taking this medicine without telling your doctor?

   Yes *1*

   No *0*

3. During the past week, did you decide to take more or less of this medicine than you were supposed to without telling your doctor?

   Yes *1*

   No *0*

4. Did you forget to take any of this medicine yesterday?

   Yes *1*

   No *0*

5. Did you forget to take any of this medicine the day before yesterday?

   Yes *1*

   No *0*

6. Did you forget to take any of this medicine 3 days ago?

   Yes *1*

   No *0*

7. Are the instructions on how to take this medicine confusing to you?

Yes *1*

No *0*

8. Did you have a hard time paying for this medicine the last time you bought it?

Yes *1*

No *0*

9. Are you thinking about stopping this medication because of concerns about side effects?

Yes *1*

No *0*

If you think you are having a serious side effect from your medicine, you should contact your doctor as soon as possible.

[Insert sentence specific to information about prescribed study medication]

You should talk to your doctor if you have any questions or concerns about your medicine.

Please click on the submit button below. Thank you for answering our questions.

Attachment 3. Example Health Literate MedSheet

SOME IMPORTANT THINGS TO KNOW ABOUT YOUR MEDICATION	
Brand Name	Humulin R U-500 KwikPen
Also Known As	Concentrated regular insulin (500 units per mL)
Purpose	This medicine lowers blood sugar in diabetic patients.
Benefit	This medicine treats high blood sugar. Maintaining healthy blood sugar levels can help prevent damage to your eyes, kidneys, nerves, and heart.
How to Take	▪ THIS MEDICINE IS FIVE TIMES STRONGER THAN REGULAR HUMULIN R. YOUR DOSE WILL BE DIFFERENT. ▪ Talk to your doctor to learn how to inject and store this medicine. ▪ Inject this medicine under the skin in your upper arm, thigh, or stomach, as directed by your doctor. Make sure to change the site where you inject the medicine each time. Do not inject into a vein or muscle. ▪ Inject the medicine at the same time each day, 30 minutes before eating. ▪ Watch your blood sugar very closely during the first weeks when you start taking this medicine or after your doctor changes your daily dose. ▪ Keep away from light and heat. New pens should be stored in the refrigerator until they expire. Do not freeze. You can store used pens at room temperature.
Warnings	▪ Do not reuse needles or share needles or pens. ▪ Do not use a syringe to remove insulin from your pen. It could cause an overdose. **While you are taking this medicine:** ▪ Please call your doctor if you have very low or high blood sugar. ▪ Limit the amount of alcohol you drink.
Ask Before Use	**Ask your doctor if it is safe for you to take this medicine if you:** ▪ Are pregnant, trying to get pregnant, or breastfeeding. ▪ Have allergies to any medicines or foods. ▪ Have any specific medical conditions or health problems. ▪ Take other medicines, vitamins, herbal products or supplements. Taking certain diabetes pills with Humulin R U-500 may cause heart failure in some people.
Common Side Effects	▪ Injection site reaction ▪ Itching ▪ Rash ▪ Weight gain **Call your doctor if you have a side effect that does not go away or gets worse.**
Serious Side Effects	**This medicine could cause low blood sugar (hypoglycemia). Some signs of low blood sugar are:** ▪ Nausea and vomiting ▪ Tremor or shaking ▪ Feeling dizzy or drowsy ▪ Blurry vision ▪ Confusion ▪ Sweating more than usual **This medicine could cause low potassium levels (hypokalemia). Some signs of low potassium levels are:** ▪ Unusual muscle pain and your muscles feel weak ▪ Very bad muscle cramps ▪ Heartbeat that does not feel normal **You could be allergic to this medicine. Some signs of an allergy are:** ▪ Swelling of face, lips, tongue or throat ▪ Hard time breathing or swallowing ▪ Very bad rash or itching **These side effects might be signs of a serious problem. If you have any, stop taking your medicine and call your doctor or 911 right away.**
For More Information	It is important to read all the additional information about your medicine you get from your pharmacy. If you have questions, ask your doctor or pharmacist. You can find more helpful information at www.nlm.nih.gov/medlineplus

Attachment 4. Study Drugs

Generic (Brand) Name	miglitol (Glyset)
Insulin	acarbose (Precose)
U200	
U300	nateglinide (Starlix)
U500	repaglinide (Prandin)
Glargine (Lantus)/Glargine (Basaglar)	
Glargine (Toujeo Solostar, Toujeo Max Solostar)	
Detemir (Levemir)	pioglitazone (Actos)
Degludec (Tresiba)	rosiglitazone (Avandia)
Lispro (Humalog)	
Insulin Regular Human (Humulin)	glipizide+metformin(Metaglip)
	glyburide+metformin (Glucovance)
Sitagliptin (Januvia)	metformin and saxagliptin(Kombiglyze XR)
Saxagliptin (Onglyza)	metformin+pioglitazone (Actoplus MET)
Linagliptin (Tradjenta)	metformin+rosiglitazone (Avandamet)
Alogliptin (Nesina)	metformin+sitagliptin(Janumet)
Exenatide (Byetta, Bydureon)	bromocriptine (Cycloset, Parlodel)
Liraglutide (Victoza)	
Lixisenatide (Adlyxin, Lyxumia)	Ixekizumba (taltz)
Dulaglutide (Trulicity)	
	teriparatide (forteo)
Canagliflozin (Invokana)	parathyroid hormone (natpara)
Dapagliflozin (Farxiga)	Abaloparatide (tymlos)
Empagliflozin (Jardiance)	
	etanercept (Enbrel)
Glimepiride (Amaryl)	adalimumab(Humira)
Glyburide (DiaBeta, Micronase, Glynase)	abatacept(Orencia)
Glipizide (Glucotrol)/ Clipizide XL (Glucotrol XL)	
Chlorpropamide (Diabinese)	
Metformin (Glucophage, Glumetza, Glucophage XR, Glumetza XR. Riomet, Fortamet)	