Regimen Education and Messaging in Diabetes (REMinD)

PROTOCOL TITLE:

EHR-based Universal Medication Schedule to Improve Adherence to Complex Regimens

SHORT TITLE:

Regimen Education and Messaging in Diabetes (REMinD)

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VERSION NUMBER:

Version 18

VERSION DATE:

June 28, 2021

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1.0 Objectives

We will leverage increasingly available technologies to impart a Universal Medication Schedule (UMS) in primary care to help patients living with diabetes safely use and adhere to complex drug regimens. We will conduct a 3-arm, multi-site trial to:

1.1 Specific Aims:

1. Test the effectiveness of the UMS, and UMS + SMS text reminder strategies compared to usual care.
2. Determine if the effects of these UMS strategies vary by patients' literacy skills and language.
3. Using mixed methods, Evaluate the fidelity of the two strategies and explore patient, staff, physician, and health system factors influencing the interventions.
4. Assess the costs required to deliver either intervention from a health system perspective.

1.2 Hypotheses:

1. Compared to usual care, patients receiving the UMS or UMS+SMS text reminder strategies will demonstrate a better understanding of how to safely dose their Rx regimen
2. Compared to usual care, patients receiving the UMS or UMS+SMS text reminder strategies will when possible, take their Rx regimen fewer times per day
3. Compared to usual care, patients receiving the UMS or UMS+SMS text reminder strategies will have greater adherence to their Rx regimen
4. Compared to the UMS only arm, patients receiving the UMS+SMS strategy will have greater adherence to their Rx regimen.
5. The intervention effects will be greater among those with limited literacy and English proficiency.

2.0 Background

2.1 The Challenge of Managing Complex Drug Regimens:

In ambulatory care, patients assume primary responsibility for safely and appropriately administering R_x regimens. Yet the expectations placed on patients by the healthcare system for medication-related tasks are considerable. In order for patients to gain the benefits of drug therapy while minimizing risks of adverse drug events (ADEs), they must: 1) have a functional understanding of medications and their proper dosing, 2) consolidate their regimen to the most efficient daily schedule, 3) problem-solve around regimen use as changes occur, and 4) continue the behaviors

over time. Studies have repeatedly documented that patients have problems performing these routine tasks. This is alarming, as adults are being prescribed increasingly complex medication regimens. Over the past decade, the percentage of Americans taking ≥ 5 R_x drugs daily has doubled to nearly 40% of older adults. While long-term adherence is essential to reap health benefits, all forms of non-adherence - failure to fill new prescriptions, incomplete use, and premature discontinuation - are common. Non-adherence has been linked to greater morbidity and mortality from chronic conditions. Complex drug regimens also raise the risk for errors and ADEs, many of which are preventable or ameliorable. 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, among older patients, and those with multi-morbidity.

The Case of Type 2 Diabetes. The increasing number of individuals living with type 2 diabetes (estimated at 10% of the U.S. adult population) must contend with extended duration, multi-drug regimens to manage the disease. These regimens often require frequent dosage changes and have formidable potential side effects (e.g. hypoglycemia) that may intentionally – or unintentionally – distract one from proper medication use. Yet these patients are also likely to have comorbid conditions, such as hypertension and hyperlipidemia that require additional medications, further complicating daily R_x regimen schedules. In a study of 13,365 type 2 diabetic adults, Chen et al. classified 38% as having moderate to major polypharmacy concerns. A significant, gradient association was found between increasing polypharmacy and higher rates of non-adherence to oral anti-diabetic drugs (measured via refill, proportion of days covered).

Age, Literacy, and Language as Risk Factors. Older age poses a significant risk for medication safety and adherence concerns. The prevalence of multi-morbidity increases with age; approximately 17% of younger adults ages 20-39 live with 2 or more chronic conditions compared to a third of middle-aged adults (40-59), and nearly two thirds of individuals over 60 years old. This, in turn, often translates to a greater number of prescribed medications. As part of the aging process, the challenge of managing complex R_x regimens is made ever more difficult by higher rates of cognitive decline and limited health literacy.

Numerous studies have found limited literacy skills to be significantly associated with patients' poorer recall of medication names and indications, inadequate understanding and demonstrated use of R_x instructions and precautions.[5,6,32-37] Our team also found that patients, especially those with lower literacy, may overcomplicate multi-drug regimens by taking medicine more times a day than necessary.[4] While studies are inconclusive as to whether lower literacy is associated with non-adherence,[38-41] evidence clearly suggests lower literate patients are more likely to misunderstand R_x instructions, putting them at greater risk.[7,42]

In addition, limited English proficiency (LEP) presents a formidable barrier in healthcare.[43-48] Interpreters are rarely available to aid physicians and pharmacists in

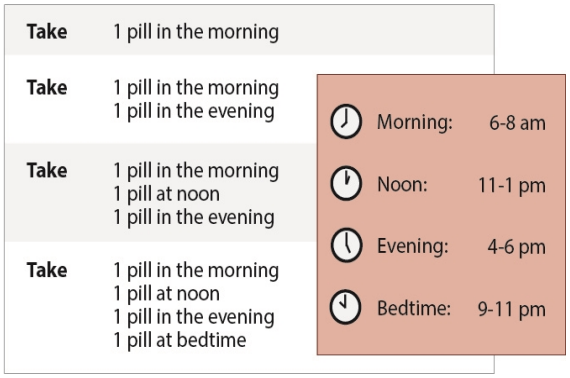
counseling LEP patients on safe R_x use, instructions are frequently unavailable in non-English languages, and multilingual materials are often inaccurate and poorly translated.[49-52] These barriers have a deleterious effect on LEP patients' R_x use.[53-55] Wilson et al. found among 1200 LEP adults, half had difficulties interpreting R_x instructions and 16% reported an ADE.[55] Similarly, Sleath et al. found that 58% of LEP adults misinterpret English R_x instructions.[56]

Health System Barriers. Individual barriers such as older age, limited literacy, and LEP are exacerbated by health system barriers.[57] Multiple studies have shown physicians often fail to discuss with patients basic information around the safe use of prescribed medicines, let alone other relevant concerns (i.e. cost of medications).[58-62] Furthermore, print R_x information is rarely distributed at the point of prescribing. Evidence also suggests that pharmacists equally fail to counsel patients on safe and appropriate R_x use.[58,60,61] While print materials (R_x labels, warning stickers, Medication Guides, patient leaflets) are provided by pharmacies, most are poorly written and confusing.[63-66] In addition, considerable variability has been identified across this process.[67-69] Bailey et al. found R_x instructions written by physicians to be highly variable;[68] Wolf et al. reviewed R_x instructions printed by multiple pharmacies and also found that pharmacy translations often deviated from physicians' instructions.[69] *Variable, poor quality physician prescriptions and pharmacy translations and lack of appropriate counseling complicate the task of organizing and properly dosing multi-drug regimens.*

2.2 An Evidence-Based Solution: A Universal Medication Schedule:

The IOM 2008 report *Standardizing Medication Labels* recognized the need to set standards for prescribing and dispensing practices to promote safe and accurate medication use.[70] Members of our research team (Wolf, Wood) presented the UMS concept in this report. As nearly 90% of prescriptions are taken 4 times a day or less, the UMS specifically proposed to establish 4 standard time intervals (morning, noon, evening, bedtime) for the prescribing and dispensing of medicine. This would remove current variability in the way prescriptions are written by physicians and transcribed by pharmacists.[67-69] All prescriptions would instruct patients to take their medicine at one or more of these specified times; this would be described in a single, standardized fashion (**Figure 1**). UMS instructions also use health literacy best practices, like simplified text, numeric characters instead of words to detail dose (1 instead of 'one'), and carriage returns (placing each dose on a separate line) to clearly identify every time a medicine is to be taken.[4]

Figure 1. The Universal Medication Schedule (UMS)



There is strong evidence supporting the UMS.[4,70-77] Among a multi-site sample of 500 primary care patients, Wolf et al. found those receiving UMS instructions versus a current standard were 33% more likely to accurately interpret R_x instructions.[72] Lower literate adults were more likely to correctly comprehend the UMS instructions. These findings were replicated among 94 patients in Cork, Ireland, and also among 203 LEP patients in Chicago and San Francisco.[73,74,78] Earlier studies also found the use of more explicit time intervals, such as those used in the UMS approach, improved patient understanding and reduced medication errors.[72,79]

Our team recently completed a clinical trial testing the UMS as an embedded standard in pharmacy practice [R01HS017687; R01HS016435]. 845 English and Spanish-speaking, low-income patients with type 2 diabetes and hypertension being cared for by one of 8 community health centers in the Washington D.C. area received reduced-cost medications from a collaborating non-profit, central-fill pharmacy. Patients were randomized to receive their bundled medications with UMS label instructions or a current standard modeled after a leading national pharmacy chain (no orientation to UMS provided). Over 9 months, English and Spanish-speaking patients improved their proper use of multi-drug regimens (OR 1.98, 95% CI 1.02-3.85) and had a near 2-fold increased adherence rate measured by pill count (OR 0.58, 95% CI 0.35-0.98). Exploratory analyses found a non-significant trend for glycemic control (tight control (HbA1c <7.0%: 56% (UMS) vs. 46% (Standard), p=0.15). As with prior studies, these benefits were greatest for lower literate adults and those taking >5 R_x drugs. *The IOM has repeatedly highlighted the UMS; the US Pharmacopeia, American College of Physicians and National Council for Prescription Drug Programs recommend it as a standard; and California passed legislation in 2011 stating the UMS as a best practice for R_x labeling, also supported by the National Board of Pharmacy.*[70,80,81]

2.3 Shifting Upstream: Implementing the UMS at Prescribing vs. Dispensing Medication:

The above AHRQ/NIH-funded trials revealed several obstacles: 1) over half of patients routinely use multiple pharmacies resulting in their continued receipt of variable R_x label instructions, 2) imparting the UMS only on drug labels was not a sufficient signal to patients to consolidate multi-drug regimens, 3) patients need comprehensive views of the UMS applied to their entire R_x regimen vs. individual R_x labels only, and 4) additional reminders may be beneficial to reinforce UMS prescribing after medical encounters, helping patients remember and simplify daily R_x use, and support adherence. Both pharmacy and patients expressed a need for improved, plain language R_x information that provides general knowledge to support safe R_x use. Our proposal is based on evidence from the field, extensive experience with EHRs, mobile technology, and funded development work [R18HS17220, R21CA132771, R01NR011300, R01NR012745, U19HS021093, California Endowment, California Healthcare Foundation]. We will shift the implementation of the UMS to primary care, leveraging technologies that are increasingly prevalent per federal mandates (Health Information Technology for Economic and Clinical Health

(HITECH) Act), particularly among community health centers.[82] We respond to the Office of the National Coordinator 'Meaningful Use' criteria by leveraging an EHR to impart standard, patient-centered information supporting safe R_x use.[83]

2.4 Leveraging Increasingly Available Technologies to Support Medication Use:

Technological solutions are increasingly available that can be leveraged to help patients learn how to safely and appropriately take prescribed drugs that are not cost-prohibitive, such as EHRs and SMS text messaging.[82,84-86]

'Meaningful Use' of EHRs. Now in the second stage of the Office of the National Coordinator (ONC) 'Meaningful Use' criteria that establishes incentives and directives for leveraging EHRs in practice, the proposed UMS interventions are directly responsive to the upcoming third stage criteria (2016) that seek ways that physician practices can use their EHR to improve: 1) quality, safety, and efficiency leading to improved health outcomes, and 2) patient access to self-management tools.[83] Our team has successfully field tested the UMS strategy at two academic centers using different EHR platforms (EpicCare: R18HS17220, R21CA132771; Cerner: U19HS021093).[84] This included: 1) UMS-mapped standard physician instructions (a.k.a. 'sigs') that were e-prescribed to pharmacies (Epic only), 2) plain language medication information sheets ('MedSheets') incorporating the UMS sig given to patients upon checkout, and 3) a redesigned EHR medication list ('MedList') that organized a patient's entire R_x regimen according to UMS intervals (Cerner only). All of these tools were co-developed by physicians, nurse practitioners, nurses, and clinic administrative staff to ensure all would not negatively impact clinic workflow and efficiency. The intervention includes UMS sigs and decision support tools for asthma, which have been developed, vetted by providers, and successfully piloted at Mt. Sinai.

Mobile Technologies to Promote Health Behavior Change. While EHRs can be leveraged to provide tools to support appropriate medication use in primary care, additional measures may be necessary to promote safe medication use outside of healthcare settings.[84,87] Mobile technologies, specifically SMS text messages, have been used to provide health-centered messages to patients in their daily lives.[88-91] Recent estimates indicate mobile technologies are useful tools for reaching low-income populations and racial/ethnic minorities; 92% of African-American and Latino adults own cell phones.[92] Text messaging capabilities are also commonly used; 81% of cell phone users send or receive text messages.[92] *While use of this technology is more common among younger adults, the number of older adult cell phone (even smart phone and tablet) users is increasing exponentially (89% ages 50-64; 77% ≥65), including those who actively receive and send text messages.*[92]

Multiple studies have evaluated text messaging as a means to change behavior.[87,88,93] Cole-Lewis & Kershaw evaluated 12 interventions that utilized text messaging as a platform for disease management or prevention.[88] Eight studies reported positive changes in among individuals receiving text messages for outcomes including weight

loss, smoking cessation, blood glucose monitoring and hemoglobin A1c. Recent studies have found text reminders increased R_x adherence, yet causal mechanisms and 'best practices' remain unclear.[94,95]

3.0 Inclusion and Exclusion Criteria

3.1 Patient Inclusion Criteria:

1) 21 or older, 2) Type 2 diabetes mellitus diagnosis, 3) Seek care at family medicine or general internal medicine practices in the Chicago-land area (Northwestern) or New York City (Mt. Sinai), 4) English or Spanish speaking, 5) Take 5 or more prescription drugs for chronic conditions, 6) Adequate visual acuity and hearing, 7) Adequate cognitive capabilities to consent to participate, 8) primarily responsible for administering their own medication, 9) own a cell phone and are comfortable receiving text messages, 10) most recent hba1c value ≥7.5%.

3.2 Provider Inclusion Criteria:

1) Resident, Attending Physician or Mid-level provider (NP, PA, pharmacist) working in General Internal Medicine, primary care, or family practice clinics within NMHC, Northwestern Medical Group, or NM Regional Medical Group (RMG) during study dates.

3.3 Adults unable to consent, individuals under the age of 21, and prisoners will be excluded from this research.

3.4 COVID-19 Survey Eligibility:

Wave 1: We will include any participant who has consented to participate in the main study and who has indicated that they were willing to be contacted for future studies run by Dr. Wolf on the consent form.

Waves 2 – 4: We will include any participant who has consented to participate in the main study, who has indicated that they were willing to be contacted for future studies by Dr. Wolf on the consent form, and who completed at least Wave 1 of the COVID-19 survey.

Waves 5 – 9: We will include any participant who has consented to participate in the main REMinD study, who has indicated that they were willing to be contacted for future studies by Dr. Wolf on the REMinD consent form, and who completed at least Wave 1 of the COVID-19 survey.

4.0 Study-Wide Number of Subjects

4.1 A total of 900 patients will be enrolled in the study across all sites; about 450 from Northwestern and 450 from Mt. Sinai.

4.2 We expect 450 providers will be enrolled, 225 at each site.

5.0 Study-Wide Recruitment Methods

5.1 Both Mount Sinai and Northwestern will follow similar recruitment methods. The general strategy for recruitment is described here, and a more detailed description of the recruitment methods specific to Northwestern are detailed in section 22.0.

At both sites, potential participants will be identified through reports generated by the Enterprise Data Warehouse (EDW). Study staff will review the charts of identified patients to confirm eligibility that cannot be ascertained via the EDW. Among the remaining eligible patients, physician consent will be obtained to contact potential participants on their behalf. Research staff will mail patients a letter informing them of the study with the option to opt out via a toll-free number (see Recruitment Letter). Seven days after the initial mailing, a Research Coordinator will contact potential subjects by phone. Eligibility of patients will be determined from screening questions administered at this time (see Screener).

6.0 Multi-Site Research

6.1 Northwestern is the lead coordinating center for this project. Mt. Sinai is the second site of this study (Mt. Sinai Medical Center (MSMC)). Study personnel (specific names and training discussed in sections 9.4 and 20.1) will follow identical procedures to those described in the Northwestern protocol and in-person recruitment procedure in section 22.1. The Mt. Sinai approval letter is included in the IRB application.

6.2 The entire research team will meet by conference call bi-monthly before the study battery is fielded to discuss logistical issues, refinement of survey, and other issues pertaining to the study. Throughout the study Drs. Wolf and Federman will conduct weekly team meetings by conference call. This time will be used to discuss progress of the study, discuss any changes that may need to be made to the protocol or study battery. The project manager will email any modifications to the IRB protocol to the Mt. Sinai PI and research coordinator within one day of receiving approval. Following approval at the Mt. Sinai site, the research coordinator will email a copy of the amendment approval letter. The Mt. Sinai PI will abide by their institution's policies. Additionally, the project manager will hold weekly meetings with project staff to ensure that the protocol is being followed.

7.0 Study Timelines

Timeline:
We are anticipating the project to be completed in 5 years. The image below describes the timeline of events for this proposed study.

Study Timeline

TASK	YEAR 1		YEAR 2			YEAR 3		YEAR 4		YEAR 5	
Convene DSMB											
Develop, pilot test and refine assessment tools											
Implement, de-bug EHR tools											

Recruit, consent, and randomize participants											
Conduct baseline interviews											
Conduct follow-up interviews											
Seek feedback from clinic staff											
Extract EHR data											
Clean and analyze data											

Study Duration:

1. The anticipated duration of participation will be 6 months. Patients will complete an in-person or phone interview at time of consent and enrollment. They will then complete 3-month and 6-month post baseline interviews.
2. We have allotted 36 months to recruit and enroll all participants.
3. We anticipate 9 additional months to finish preliminary analysis. The estimated date to complete analysis is the end of July 2022.

8.0 Study Endpoints

8.1 The primary study endpoint will be the completion of all analyses of the Aims. A secondary study endpoint will be when all enrolled and retained participants in the trial (n=900) complete up to 6 months of follow up interviews.

9.0 Procedures Involved

9.1 We will conduct a 3-arm randomized controlled trial to test the effectiveness of UMS interventions to improve safe use and adherence to complex R_x regimens. The research at Northwestern will take place in the Primary Care, Family Medicine or General Internal Medicine clinics at Northwestern Memorial HealthCare (NMHC), Northwestern Medical Group and Northwestern Medicine Regional Medical Group. Recruitment will also be done at Mt. Sinai Medical Center (MSMC), which will be monitored by their IRB. Northwestern, as the lead site, will also be overseeing recruitment at both sites.

9.2 Intervention-related Aspects:

9.2.1 Randomization. As the UMS EHR 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 level (N=500 eligible clinicians; ~250 per site). This is possible with Epic; we can 'turn on' or off these UMS functions via physician preferences, preventing usual care physicians from having access. All consented providers will subsequently be randomized to one of the 3 study arms: **usual care**, **EHR**, or **EHR+SMS**. This process will result in a trickle down of some components of the intervention being given to patients seen by the consented provider, but not enrolled in the study for follow-up purposes (EHR tools, but not SMS). To address this, prescribers will be consented with the understanding that the care of the patients may be altered, although any risk is minimal given the educational nature of the EHR tools. This 'turning on' an EHR intervention with physician randomization has been previously approved by the IRB at Northwestern University for 3 other AHRQ grants [P01HS021141-01,

1U19HS021093-01 & 1R18HS017220-01]. All providers in the study will be approached prior to study initiation to provide informed consent. In all 3 studies, 100% of providers agreed to participate. To optimize the likelihood of obtaining similar populations in each study arm, physicians will be placed into four groups based on workload (full vs. part time) and health center (NMHC, NM RMG, or MSMC). Ms. Curtis, blinded to physician identity, will assign physicians per strata using a random number generator.

9.3 **Clinic Space, Orientation and Workflow.** Prior to implementation, Drs. Wolf and Federman will meet with physicians and staff at each site to familiarize them with the planned study activities, answer questions, elicit feedback provide a printed synopsis of the protocol per site, and give contact information. They will work closely with clinic staff to coordinate activities and plan space needs for recruitment and study visits. A patient flow chart will be developed to detail optimal timing of interventions, recruitment and data collection.

9.4 **Spanish Translation.** All of the measures identified already have Spanish versions. However, we will use a modified committee approach to translate remaining components (introduction prompts, item probes, etc.), consent and recruitment materials to Spanish. Three bilingual, bicultural translators will independently translate a third of each document to Spanish. They will then discuss the resulting texts and reach an agreement on best words and phrases for a final product. The strength of this approach has been recognized by the Census Bureau.[125] An experienced moderator (Dr. Schoua-Glusberg) will guide discussions and answer any questions about the study. We have used these methods previously in translating UMS tools.

9.5 **Pilot-testing and Refinement of Study Materials and Protocol.** We will pilot-test the study battery, protocol and patient materials among English and Spanish-speaking patients at NMHC and MSMC. Cognitive interviews will be conducted among a convenience sample of 30 patients (n=15 per language) that meet eligibility criteria to refine and standardize the study materials. We will obtain average interview completion times, 2) elicit patient comprehension and acceptability of the battery and materials. If problems are identified, root causes will be analyzed and modifications made as appropriate prior to full-scale implementation

9.6 **EHR UMS Interventions**

EHR UMS Tools. Patients in all intervention arms will receive UMS-related tools at their primary care visit along with a brief UMS orientation (by RA) to support Rx use. These materials have previously been successfully piloted in multiple NIH-funded studies.

1. UMS Rx Instructions ('Sigs').
2. MedSheets. Patients will receive single-page, plain language Rx information sheets following health literacy best practices with content appropriately sequenced from a patient's perspective (drug name, indication, purpose/benefit, how to take, for how long, when to call your

doctor, when to stop taking and call your doctor, important information). These sheets pull in the UMS sig to tailor content and serve as a tangible, 'patient-friendly' addition to the after-visit summary.

9.7 **SMS Text Reminders**. For those patients receiving text reminders (EHR+SMS), daily text reminders will be sent for 7 days post baseline interview and following any new prescription or significant change to their regimen. The premise for the week timeframe is to help patients develop a routine for weekdays as well as weekends, when schedules may be less regimented. Continuing the SMS text reminders indefinitely runs the risk of being ignored, irritating patients, and/or adding an unwelcome expense for patients (challenging sustainability for those without unlimited texting plans). We will use an affordable, safe, premium internet SMS text service plan (EzText) to program and schedule discrete UMS-centered text messages at standard intervals for all patients based on their regimen (i.e. 1, 2, 3, or 4 times daily); patients can alter the default time points of 7:00am, 12:00pm, 5:00pm, and 10:00pm. Generic reminders are used, as the SMS text message itself is a memory support sent around the general time of the behavior. The premium plan ensures patients do not receive promotional messages with the text, and a toll-free number will be provided to patients in this study arm where they can contact us to request to cancel the service if desired, or even extend it to a daily service. An RA will orient and confirm patients can retrieve text messages, and instruct them to abstain from reading texts while driving. See Appendix for more examples of texts with common mobile phones.

9.8 **Usual Care.** For this arm, current usual care includes variable physician prescribing and/or nurse counseling, no standard distribution of Rx information or use of UMS, variable or limited distribution of Rx information in corresponding pharmacies, and no active SMS or surveillance of medication use post-visits.

9.9 **Research-related Activities**: Research related activities will include both face-to-face and telephone interviews, as well as medical chart extraction. Specific details about each research activity follow below. Data collected from face-to-face and telephone interviews will be collected using REDCap, a secure, web-based application for data collection for research studies.

Baseline Interview:

At the first interview we will ask questions about the participant's diabetes history, and self-management behaviors related to their diabetes and medication related behaviors. We will also collect standard sociodemographic information. Participants will also complete a cognitive assessment if the interview is completed in-person. The cognitive assessment will not be completed if the baseline interview is completed over the phone.

If the baseline is completed in-person, research coordinators will also perform standardized measurements of blood pressures and pulse using an automated device (validated Omron HEM-907XL or a device with comparable accuracy). Three recordings will be performed at each visit and the mean of the second and third readings will be used to indicate the blood pressure for that visit. Patient positioning, arm selection, cuff size selection and other techniques will follow the procedures for

blood pressure measurement of the National Health Examination and Nutrition Survey. Blood pressure readings will not be performed if the baseline is completed over the phone.

During the interview the research coordinator will also look at how the participant is taking his or her medications. The research coordinator will count the number of pills within the participants' medicine bottles using a standardized protocol. Prior to beginning, the RC will put on gloves and will sanitize the automatic pill counter and counting stick. While wearing gloves, the coordinator will pour the entire bottle onto the automatic counter. The pill counter will automatically transfer the pills into the bottom compartment and will count the pills as they are transferred. Once the pills are in the bottom compartment, the coordinator will return the pills back into the bottle. The coordinator will place the cap on the bottle, making sure the cap is securely in place. For phone interviews, RCs will read a standardized script to ask patients to count study pills using a standardized procedure. If able, participants will be asked to join a video call so the RC can take a screen shot of the patient's remaining pills-per bottle. The RC will save the screen shot/photograph to the study project folder within the secure GIM server only using the patient's studyid to identify the photograph. No PHI will be captured in the photograph. If the participant does not have video capabilities, the RC will proceed to explain how the patient can count their pills and relay the number to the RC. This script is outlined in the interview script.

This interview will take place in-person in a private room in the clinical offices of the Family Medicine, Primary Care, or General Internal Medicine of NMHC, Northwestern Medicine Regional Medical Group, Northwestern Medical Group, Northwestern Medicine Grayslake, Northwestern Medicine Lake Forest, Delnor Hospital, Northwestern Medicine affiliated clinics, or in community sites in the participant's neighborhood (i.e. private study rooms in libraries). For interviews that are not able to be completed in-person, the RC will complete the interview over the phone from a closed office/private room. The interview will take about 90 minutes to complete.

<u>Follow up Interviews (3 months, 6 months)</u>

Participants will also be asked to participate in two follow-up interviews at 3 months and 6 months post-baseline interview.

The 3 month interview will take place over the phone and patients will be asked additional questions about how they take their medicines, their diabetes as well as gather information about receipt of UMS tools, filled prescriptions and text reminders.

The 6 month follow-up interview will take place in-person or over the phone and will gather information about receipt of UMS tools, filled prescriptions, text reminders, self-report of physician medication-related communication at recent encounter as well as complete 3 additional blood pressure readings, and the pill count. The blood pressure reading will be excluded if the interview must be completed over the phone. If the interview is completed over the phone, the same pill count protocol for baseline will be followed for 6 month. For patients consented before May 19, 2020, a brief

script will be read informing patients of the change in the consent in regards to the pill count. The RC will ask the participant to provide verbal consent to allow the study team to take a screen shot/photograph of the patient's pills during a video call in order for the RC to count the pills after the interview. The patient will be notified that no PHI will be captured in the photograph.

At the 6 month interview, in addition to the activities that will take place during the 3 month interview, patients from the intervention arm will also be asked additional, semi-structured questions to explore 1) personal challenges with regimen adherence, 2) perceived value of the EHR and SMS tools, 3) unmet needs and acceptability of other tools and approaches to support medication use.

Clinic Staff Feedback

Among consenting physicians, we will ask physicians to complete a brief survey about their experience using the tools. (See Provider feedback survey)

Medical Record Extraction:

Additional chart data will be abstracted via an additional EDW report including patient medications, chronic conditions, COVID-19 diagnosis an/or results of antibody test, and healthcare utilization (ED, hospitalization, primary care appointments) as well as hypertension, diabetes and cholesterol clinical values. Furthermore, we will extract whether patients received prescription orders in UMS format (with after-visit summaries) and the corresponding. We will also note when (days post visit) the Medication reconciliation sheet was incorporated into the EHR.

Field Notes:

The project manager will meet monthly with clinic administrators to document any changes that might have occurred and when. This will include relevant change to clinic staffing, workflow, EHR, or any significant event that could potentially alter the delivery and subsequent effectiveness of intervention. The project manager will keep a document of this.

Retention Activities:

In order to maintain high retention of enrolled participants we will mail holiday cards to participants annually. In addition, if we are unable to contact enrolled participants we will mail or email "Trying to Reach You" letters to re-engage participants. Data sources for this study will include in-person and telephone interviews with participants (see attached surveys), and medical record data extraction via the EDW.

For patients that complete COVID-19 Waves 5-9:

★ **Patient Interviews.** Participants will complete up to five telephone interviews in total, with one interview taking place every 4 months. New, supplement-specific data collection related to COVID-19 will be collected via telephone interviews; this survey is equivalent for both Aim 1 and Aim 2 activities, as data collection will be conducted in parallel.

★ **EHR data.** Medical record data will be collected via the Electronic Health Record (EHR) from January 1, 2019 - present. EHR data will confirm comorbidities

and medications. We will also extract clinical outcomes (HbA1c, diastolic and systolic blood pressure, cholesterol (LDL, HDL, total, triglycerides), GFR, COVID-19 lab tests and results, COVID-19 diagnosis, COVID-19 vaccine type and dates, and antibody results), preventive services utilization (cancer screening, immunizations), and health services use (clinic visits (including telehealth), medical subspecialty visits, emergency department visits, hospitalizations). Lastly, we will collect patient portal usage.

★ **Pharmacy fill data.** Participants will be asked if they use Walgreens or CVS to fill their prescriptions. During the consent process, participants will be informed that Walgreens and CVS Pharmacy may access, receive, or use their personal information, based on the pharmacies they utilize.*Data Collection:*

All interview measures and timepoints are listed in the table below.

Variable	**Instrument(s) or Measure(s)**	**Source**	**Timing & Window**		
			0	**3M**	**6M**
				60 - 120 days	**5M - 8M?**
Outcome Measures			**In-person or phone**	**Phone**	**In-person or phone**
Medication Adherence	ASK-12	Matza, 2009	x	x	x
	24-hour recall		x	x	x
	Pill Count		x		x
Proper medication use	24-hour recall		x	x	x
Medication consolidation	24-hour recall		x	x	x
Treatment knowledge	Identification of drug purpose		x	x	
Clinical outcomes	HbA1c	chart	x		x
	systolic/diastolic blood pressure	in-person	x		x
Patient Covariates					
Medication Regimen Characteristics	Prescription medication, complexity (MRCI)	George, 2004	x		x
	drug class	George, 2004	x		x
Health status	Overall Health (Global)	PROMIS	x		x
	Comorbidities	Goodman, 2013	x		x
	Depression - SF (4 item)	PROMIS	x		

Health Literacy	NVS, Brief health literacy screener	Weiss, 2005; Chew, 2008	x		
Cognitive Status	MMSE	Folstein, 1975	x		
Patient Activation	CHAI	Wolf, 2017	x		x
Social Support	Tangible Support	Wolshin, 1997	x		
Sociodemographics	Age, sex, race/ethnicity, education, income, language, English proficiency, country of origin, time in US	self-report	x		
Patient Process Outcomes					
Patient/Provider Communication	CAHPS - Providers discuss medication decisions		x	x	x
Perceived Values of EHR and SMS Tools	Open-ended questions				x
Unmet needs and acceptability of tools	Open-ended questions				x
Personal challenges with medication regimen	Open-ended questions				x
System Process Outcomes					
Receipt of UMS Materials	Receipt of MedSheet (yes/no), UMS Sigs (yes/no), MedList (yes/no)	self-report, chart	x	x	x
Receipt of SMS text reminders	Receipt of SMS (yes/no)	self-report		x	x
Intervention impact on clinic practice	Provider Survey				x
Changes throughout intervention within clinic practice	Field notes with administrative staff				
Cost Outcomes					
Initial programming cost of EHR tools			x		
Programming maintence costs for EHR					x
Running UMS technologies	Printer ink, paper, staff time		x		
SMS monthly costs			x		

9.10 **COVID-19 Survey.** We are proposing an optional sub-study to be conducted from a pool of existing studies conducted by Dr. Michael Wolf (LitCog (STU00026255), REMinD (STU00203777), COPD Multimorbidity (STU00201640), UMS Portal (STU00201639), and TAKE IT (STU00204465). Participants will be invited to participate

in an optional one-time brief (5-10 minute) telephone survey to capture one additional outcome pertaining to their knowledge, attitudes, and beliefs about the COVID-19 outbreak in March 2020. They will also be asked a series of patient-reported health literacy items. This new data will be linked with participant characteristics from the parent study. Participants who complete to COVD-19 survey will receive a $10 gift card in the mail.

Recruitment will be done by phone by trained Northwestern RAs. We will contact anyone who has indicated that they were willing to be contacted for future studies run by Dr. Wolf on the consent form. Verbal consent will be obtained prior to completing the one time brief (5-10 minute) telephone survey.

Waves 2-4:
From the same pool of existing studies included in Wave 1, any participants who completed the Wave 1 COVID-19 survey will be contacted and invited to participate in up to 3 additional telephone surveys (10-30 minutes each) over the course of 4 months to continue to evaluate knowledge, attitudes, and beliefs over time about the ongoing COVID-19 pandemic. Participants who complete the follow-up interviews will receive a $10 gift card in the mail for wave 2 and a $15 gift card for waves 3 and 4 (per survey), for a total of up to $40 for the follow-up activities. For wave 3 and 4, we increased the participant compensation from $10 to $15 due to the longer survey administered at this time point.

Recruitment will be done by phone by trained Northwestern RAs. We will invite anyone who has indicated that they were willing to be contacted for future studies run by Dr. Wolf on the consent form and who completed the Wave 1 survey. Verbal consent for the follow up waves will be obtained prior to completing the Wave 2 telephone survey (initiated 2 weeks after Wave 1). Participants who consent to these follow-up activities will be re-contacted for completion of Waves 3 and 4 at 1 month and 3 months post-wave 2.

Waves 5-9:
In March 2020, we recruited a subset of the REMinD cohort (n=136), and patients enrolled in four other studies (n=537; Total N=673) to form the Chicago COVID-19 Comorbidities (C3) cohort study. We initially completed four phone interviews (described above) with them to better understand how older adults with underlying health conditions, at greater risk for COVID-19 complications, were responding and taking action (or not) to prevent infection and disease spread.

We will now continue our investigation to better understand the longer-term impact of COVID-19. From the same pool of existing studies, any participants who completed the Wave 1 COVID-19 survey will be contacted and invited to participate in up to 5 additional telephone surveys occurring every 4 months. Interviews will collect information on participants' responses to COVID-19 and changes in lifestyle behaviors, healthcare utilization, physical and mental health, access and adherence to treatment, socioeconomic circumstances and clinical outcomes. We will also collect data from the medical record and pharmacy record abstractions.

Participants who complete additional telephone surveys will receive compensation in the mail. See section 22.2 for further details.

Data from all waves of the COVID-19 telephone surveys will be captured in REDCap.

this study (STU00208130) in order to create a final and complete dataset..

10.0 Data and Specimen Banking

10.1 Participant data will be collected using the Northwestern-based REDCap survey platform and Northwestern's Sharepoint (for EHR extraction data) and all data will be stored under an ID number. 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. Data will be stored on Northwestern encrypted servers and access will be granted through the PI.

11.0 Data and Specimen Management

11.1 Analysis Plan – Aim 1

The proposed trial uses stratified randomization with random block size to achieve group comparability and balance. Stratified by clinic, and provider type (full time, part-time, resident) randomization occurs at the provider level, where patients are randomized to the same group as their provider. Each provider (approximately 201 across the 2 sites, 100 per site) will be randomized to one of three arms resulting in approximately 67 physicians per arm. We will assume 4 patients per provider, and conservatively anticipate at least 80% retention for follow-up at six months. This will result in 900 participants recruited to the study with an anticipated minimum of 720 (240 patients per arm, 3 per physician) available after 6 months, contributing to primary data analysis.

To ensure adequate balance across treatment arms, baseline outcomes and potential confounders including socio-demographic characteristics, comorbidities, regimen complexity (i.e., # of medications, total pills taken daily), health literacy, and language will be compared across arms using descriptive statistics. Additionally, these variables will be examined one-at-a-time for associations with effectiveness outcomes, and those variables found to have significant associations with outcome(s) will be considered potential covariates in the generalized linear mixed models (GLMMs) used for formal analyses as described below. Backward stepwise model building approaches will be used to determine final, parsimonious model(s) for study outcome(s).

Prescription medication adherence at 6 months is the primary outcome of interest for Aim 1, with treatment knowledge, demonstrated proper Rx use, and regimen consolidation outcomes relevant to hypotheses of secondary interest. For each outcome, we will use generalized linear mixed-effects models (GLMMs) to test for the effects of EHR and SMS text reminders, specifying the proper link functions

based on the distribution of the outcome variable. The GLMMs will include random provider effects and fixed binary variables for SMS text reminder and EHR to denote the intervention groups and the usual care group (H1-4). We will include a fixed indicator variable for clinic in the GLMMs and any potential confounding covariates as noted above. Analyses will be performed using PROC GLMMIX in SAS (v.9.3) and lme4 package in R. Since understanding and adherence will be assessed for each medication, 2-level GLMM will be used with medications nested in participants. We will first test for differences in the outcomes between the EHR group and usual care (H1-3), followed by comparisons between EHR+SMS vs. usual care, and EHR vs. EHR+SMS to determine additional benefits of SMS texting (H4) by constructing contrasts.

Aim 2

We will include both literacy-by-arm and language-by-arm fixed interaction terms in the above GLMMs for all outcomes. We will use the corresponding model type III tests for fixed effects to determine significance of terms, and construct appropriate contrasts for pairwise comparisons for each literacy level and each language.

Aim 3

We will determine the extent to which the interventions were implemented as planned (a process evaluation) across each site and for all three study arms, in order to optimize the intervention for future dissemination opportunities.

Mixed methods will be employed using a convergent parallel design to obtain data on intervention implementation.

Quantitative and qualitative findings will be merged to answer 1) whether either intervention was implemented as planned, 2) from a user-perspective, do interventions require modification and how. In this approach, both analyses are conducted separately and merged for side-by-side data comparisons. For quantitative data (patient report, EHR data), frequencies will be generated to determine outcomes related to receipt of materials, perceived helpfulness of materials, CAHPS and PACIC. For CAHPS and PACIC data, similar GLMM models as described in Aim 1 analyses will be performed, with intervention arm as the primary independent variable. For qualitative data, we will review and explore the transcribed patient interviews and clinic staff discussions using content and ethnographic analysis. Predetermined categories will organize feedback from all users: patient, provider, clinic/health system. Within each of these broad categories we will use a predetermined coding approach to quantify the frequency of two subcategories: facilitating factors, and impeding factors (see Figure 8). An additional layer within impeding factors would be whether factors are modifiable or not, and under facilitating factors, if they are replicable. Field notes and quantitative findings will be integrated in this model. Transcribed interviews and field notes will be examined by the study team independently to see if modifications to the categories are needed.

Aim 4:

We will directly measure and assess the provider perspective costs of developing and running UMS interventions, alone and in combination. Incremental cost of

interventions will be estimated relative to usual care from the perspective of NMHC, NM Regional Medical Group, and MSMC practices implementing these processes and tools. First, we will document the initial costs associated with programming the EHR tools at a new site, following the code and standard operating manual guidance from Aim 3. The primary costs of running these UMS technologies in the EHR arm involves the limited expenses around printing the EHR tools (printer ink, paper, staff time) as a result of generating new Rx information with after-visit summaries. SMS monthly costs will be easily documented from EZText invoices as well as usage. However, we will include estimates for programming maintenance for Epic EHR, and will test the sensitivity of results to changes in the maintenance requirements in terms of programmer hours, calculated per site. 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.

Exploratory Analyses. We will repeat all GLMM analyses described for Aim 1 to explore whether differences in interventions vary by relevant covariates representing patient and regimen characteristics known to impact outcomes, specifically adherence. Interaction terms will be included in models accordingly. As adherence has its many measurement challenges, experts recommend triangulating with multiple measures. We will compare results across each adherence measure (ASK-12, 24-hour recall, pill count) and create a general estimate of adherence via single factor score using maximum likelihood estimation. Exploratory analyses will examine HbA1c and blood pressure from baseline to 6 months, although power may be limited. Additionally, we will construct marginal models for all primary and secondary outcomes using generalized estimating equations (GEE) in a process similar to those described for the GLMMs. The purpose is to obtain population-averaged estimates of any differences in outcomes across arms vs. estimates at participant level.

The effect of the educational tools will be assessed by comparing responses on the disease-specific questionnaires administered post-education in those undergoing standard pregnancy-related diabetes education with those utilizing the newly developed toolkit. The effect of the educational intervention will also be assessed via the primary and secondary clinical outcome variables previously described. Patient satisfaction, assessed by the CAHPS Survey, will also be compared.

Health literacy data will be analyzed and categorized as to “high likelihood of limited literacy”, “possibility of limited literacy”, or “adequate literacy’. Comparison of literacy categorizations will be made between the two populations (military and civilian). Baseline disease-specific knowledge will also be analyzed according to literacy and compared between the populations. Literacy and disease-specific knowledge will be analyzed according to demographic characteristics as described.

11.2 Sample Size.

Study sample size was based on pairwise comparisons (EHR vs. usual care, EHR + SMS vs. usual care, EHR vs. EHR + SMS) of the primary outcome of medication adherence at 6 months between the EHR and usual care study arms (Aim 1, H3). Power calculations assumed roughly 67 physicians (clusters) per arm (201 total clusters), each with approximately 4 participants, yielding a targeted 900 total participants and a conservative 80% retention rate (~3 participants per provider). All pairwise comparison type I error rates were assumed to be a conservative 1.67% (i.e., the Bonferroni correction to preserve overall type I error rate at 5%), to correct for a potential type I error rate inflation in the presence of multiple pairwise comparisons. While a low Intra-class correlation coefficient (ICC) is expected based on a lower probability of clustering either by clinic or physician (given behavior under study and ability to prevent EHR or SMS functionality in usual care), we explored scenarios where the ICC might range from 0.001 to 0.01.

Based on our 2014 findings examining the UMS in pharmacy practice [R01HS017687; R01HS016435], We expect 45% of usual care patients to be adherent at 6 months (Table 5). With prior-specified assumptions, we will have 85%-88% power to detect a minimum absolute difference between study arms of 14%. With the sample size set by the primary outcome of adherence at 6 months, we also show overall estimated detectable pairwise differences for secondary outcomes of demonstrated proper use and consolidation at 80% power (Aim 1, H1-4) based on usual care estimates for proper use and regimen consolidation.

11.3 **Protocol to ensure confidentiality:**

Each subject will tracked using an Access database. Identifiers and other related information for coordinating research activities (recruitment outcome, research 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.

Several methods will be employed to reduce the risk of breach of confidentiality. A study identification number will be assigned to each subject in the study. The research data collected and stored will have the study identification number and no other identifying information on it. The consent forms and the de-identified study data will be kept in a separate locked file cabinet at the same location. Using this method, if someone were to gain illegal access to the locked filing cabinet with study data, they would have no way to link this data to any identifying information. Mt. Sinai will do the same with their participants, under their own IRB.

11.4 **Quality Assurance:**

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). Training the entire research staff at once, via a web conference, to ensure uniform administration of the study protocols and interviews. Practice of the interviews will proceed independently at the participating institutions. All interviewers will be required to demonstrate competence in survey administration and to pass a certification test.

11.5 **Study-wide data management:**

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

Data Storage: The research staff at NU and Mt. Sinai will collect data through the Northwestern RedCap survey platform. Data will be stored in REDCap, a secure, web-based application, and on the Northwestern secure servers for the length of the study. Data from Mt Sinai's EHR extractions will be uploaded to Northwestern's Sharepoint site specific to this study. The Project Manager or Data Analyst will download the data from REDCap monthly and save to the "Analytic" folder within the 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. No identifiability information are entered into REDCap. 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 Coordination Center (Northwestern): The project manager and data analyst at NU will combine the data and maintain the master data file containing all data from each location, create a data dictionary, and be responsible for data cleaning and providing updated data to study investigators when requested.

COVID-19 Survey: By extending each of these studies (LitCog (STU00026255), REMinD (STU00203777), COPD Multimorbidity (STU00201640), UMS Portal (STU00201639), and TAKE IT (STU00204465)) to capture an additional patient-reported outcome related to one's knowledge, attitudes and behaviors related to COVID-19, we can link participants' responses to this longitudinal survey to a minimum data set of participant characteristics that include demographic, socioeconomic, cognitive (including health literacy) and health behavioral characteristics. We will then be able to investigate determinants of COVID-19 knowledge, attitudes and behaviors without duplicating data collection efforts for these variables.

Dr. Peipert will be analyzing data from the Wave 1 health literacy items.

Aaryn Phillips will be analyzing data to better understand alcohol use in older adults during the COVID-19 pandemic. Minjee Kim is an assistant professor of neurology and will be analyzing the PROMIS Sleep items to better understand the relationship between COVID-19 and sleep disturbance.

RCs will conduct interviews by telephone using REDCap survey software. Ms. Opsasnick (analyst) will oversee database structure & quality assurance. Participants will complete 5 phone interviews with RCs.

Statistical analyses will be led by Dr. Kwasny, and all analyses will be conducted with SAS 9.4 (Cary, NC). Using data from the C3 cohort, participants' perceived levels of stress has been assessed from the initial onset of the outbreak (March 13-20; C3 W1), through its rapid acceleration (March 27-April 3; C3 W2) and apex phases (May 1-22; C3 W3), and the flattening phase (July 15- August 15; C3 W4) of the COVID-19 pandemic. The additional surveys provides the opportunity to continually assess persistent stress over a span of time that likely will include the pandemic's expected, slow recovery, an anticipated second wave in the fall/winter of 2020/2021, and its eventual recovery as well. Also during this time, there may be new treatments available, as well as a vaccine for COVID-19. Initial models will examine associations between perceived stress as a result of COVID-19 and health and healthcare outcomes over time among C3 participants. As perceived stress, health and lifestyle behaviors are expected to change over time, we will use GLMMs to examine the relationship between stress, and outcomes (diet, alcohol use, smoking, physical activity, diet, weight gain, sleep, social isolation, treatment adherence, self-reported health status) using stress as a time-varying covariate. For data from the EHR, we will assess routine health care use.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

12.1 Data Safety and Monitoring Board (DSMB): The DSMB will be formed early in the project and be given responsibility to review and approve the methods and analysis plan. It will be organized by Drs. Wolf and Federman and include a biostatistician, and three clinical researchers (physician, nurse, pharmacist) with related expertise. Meetings will be held via video-conference to review protocols, procedures, and concerns related to research integrity.

13.0 Withdrawal of Subjects

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

13.2 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. They will then not be contacted for further interviews or visits.

14.0 Risks to Subjects

14.1 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 interview and discussion group 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.

15.0 Potential Benefits to Subjects

15.1 It is possible that subjects enrolled in the two 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 mobile technologies and the EHR to support safe and appropriate medication use.

16.0 Vulnerable Populations

N/A

17.0 Community-Based Participatory Research

N/A

18.0 Sharing of Results with Subjects

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

19.0 Setting

19.1 The Research Coordinator will identify and recruit potential participants who are patients at Northwestern Memorial HealthCare (NMHC) and Northwestern Medicine Regional Medical Group. In-person interviews will take place in a private office within Northwestern Medicine, Northwestern University, or in community sites in the participant's neighborhood (i.e. private study rooms in libraries).

20.0 Resources Available

20.1 The research team is comprised of 3 PhD level researchers, 5 Physician-researchers, 1 master's degree level researcher, 2 project managers, and 4 bilingual research assistants (all with experience on similar projects). The co-PIs represent two academic institutions with proven track records in health literacy, medication safety and adherence, and the use of health technologies. All team members have extensive knowledge on health literacy in the context of medication management and health technologies. Co-Investigators on this project include the Lead Technical Informaticist of Epic EMR Clinical Transformation Group, Mount Sinai Health System, and the Director of the Health Literacy and Learning Program (HeLP), which seeks to advance the study of limited health literacy and interventions that could improve one's ability to obtain, process, and understand basic information needed to make appropriate health decisions. The investigators have successfully collaborated on numerous previous projects.

Both site project managers have 5 years of experience managing complex research studies and supervising research staff. The research assistants receive extensive training on research methods, interviewing techniques and the consent process.

20.2 NMHC: The GIM clinic of NMHC has >20,000 active patients (patients with two or more office visits in the past 18 months), of whom nearly 3,000 are living with type 2 diabetes. The practice serves a diverse patient population (30% African-American, 10% Latino) and represents the entire spectrum of socioeconomic status. The practice

is comprised of 4 clinical 'pods' and employs ~40 attending physicians and 77 residents.

Northwestern Medicine Regional Medical Group: The GIM clinic of NM Regional Medical Group has over 74,000 active patients. The GIM practice within the Regional Medical Group is comprised of 14 clinics and employs ~168 physicians.

MSMC: The Internal Medicine Associates of Mt. Sinai (IMA) is the large, hospital-based general medicine practice for the Mt. Sinai Medical Center. It is comprised of 4 individual practice firms and employs ~40 full-time attending physicians, 3 general medicine fellows, and 140 residents. The practice has almost 24,000 patients; 5,000 have diabetes. IMA is located in East Harlem, NY and the demographics of its patients reflect the diversity of the surrounding communities. Both NMHC and MSMC use the Epic EHR platform. With these sites combined, we have already identified via each sites' enterprise data warehouse (EDW) 7,837 eligible patients for the study.

21.0 Prior Approvals

21.1 We have funding from the National Institute of Nursing Research. Northwestern is the primary awardee.

22.0 Recruitment Methods

22.1 This section provides more explicit detail about the recruitment methods that will be employed at the Northwestern site.

Potential participants will be identified through reports generated by the Enterprise Data Warehouse (EDW). The EDW report will list patients with an upcoming appointment in the NMHC or Northwestern Medicine Regional Medical Group GIM clinics and will contain patients name, dob, address, mrn, appointment date, appointment type, PCP. The research staff will review the charts of identified patients to confirm eligibility that cannot be ascertained via the EDW (Eligibility Criteria: 5) prescribed 5 or more prescription drugs for chronic conditions). Among the remaining eligible patients, primary care physicians will be contacted via EPIC message to request permission to contact potential participants on their behalf and to identify any patients who would not be appropriate for the study. A Research Coordinator may then contact by mail potential subjects. A mailed letter to potential participants will include detailed study information and will have the option to opt out of the study via a toll-free number (see Recruitment Letter). The letter will be mailed using NMHC letterhead. Seven days after the initial mailing, a Research Coordinator will contact potential subjects by phone. Due to COVID-19 restrictions, the study team may not be able to mail letters to all patients. If a letter mailing is not possible, the RC will still obtain permission from the provider to contact their patient and will contact the patient by phone 7 days after Epic message is sent to the provider, unless the provide declines patient contact. Eligibility of patients will be determined from screening questions administered at this time (see Screener). During the screening phone call, if a participant is interested in participating but does not want to complete the screener over the telephone they may complete the screener in person prior to the baseline interview. The participant will be informed that prior to

participating they will complete the screener, which may result in them not being able to participate. For eligible and interested potential subjects, appointments for baseline interview will be made during this phone call. Written, online, or verbal consent will be obtained at baseline.

COVID-19 Surveys Recruitment Waves 1 and Waves 2-4: Recruitment will be done by phone by trained Northwestern RAs. We will contact anyone who has indicated that they were willing to be contacted for future studies run by Dr. Wolf on the consent form and who completed the Wave 1 survey. Verbal consent for the follow up waves will be obtained prior to completing the Wave 2 telephone survey (initiated 2 weeks after Wave 1). Participants who consent to these follow-up activities will be recontacted for completion of Waves 3 and 4 at 1 month and 3 months post-wave 2).

COVID-19 Surveys Recruitment Waves 5-9: All methods of recruitment will be done by trained Northwestern RCs.

We will first mail a recruitment letter introducing the study to all eligible patients prior to contacting them by telephone. If the participant is not interested in participating or being contacted by the researcher, he/ she can opt out by calling the toll-free number within 7-10 days and the RC will not contact the participants. Due to COVID-19 restrictions, the study team may not be able to mail letters to all patients. If a letter mailing is not possible, recruitment will be done by phone by trained Northwestern RCs and will let the patient know about the opportunity to continue their participation and see if they are interested in learning more about it.

If they are interested in participating, the RC will engage patients in the informed online or verbal consent process and HIPAA Authorization, as approved by the Northwestern University Institutional Review Board. After obtaining consent, RCs will conduct the telephone interview or schedule it to be completed at a later date.

22.2 Participant Payment:

Research Interview	Payment	Form of Payment
baseline	$ 40	cash at close of in-person interview or mailed money order/gift card if phone interview
3 month	$ 10	mailed money order
6 month	$ 40	cash at close of in-person interview or mailed money order/gift card
Text message reimbursement	$10	Cash at close of 6 month interview

COVID-19 Survey: Participants who complete the wave 1 COVID-19 survey will receive a $10 gift card in the mail. Any participants who completed wave 2 will receive a $10 gift card; participants who complete wave 3 will receive a $15 gift card for their time; participants who complete wave 4 will receive a $15 gift card for their time (for up to $40 for all follow-up activities). All participants who verbally consent and complete any portion of the telephone interviews will be compensated.

COVID-19 Waves 5-9: Participants will receive the following compensation for each interview they complete:

Timepoint	Compensation
Wave 5	$20 gift card
Wave 6	$20 gift card or money order
Wave 7	$30 gift card or money order
Wave 8	$30 gift card or money order
Wave 9	$40 gift card or money order

Money orders may issued for subject compensation for COVID-19 supplement surveys if Visa gift cards are problematic for the subject.

In addition to the outlined compensation above, the study team will do an additional mailing of a pair of no slip socks and thank you letter to each participant enrolled in the COVID-19 Supplement. This is an added incentive to express our gratitude for their continued support and to help promote engagement in the remaining phone surveys.

23.0 Local Number of Subjects

23.1 A total of 450 participants will be recruited at Northwestern, with 150 participants assigned to each study arm. A total of 225 providers will be recruited at Northwestern, approximately 75 per study arm.

24.0 Confidentiality

24.1 Only authorized research personnel will have access to study related data.

Each participant will be tracked using an Access database. Identifiers and other related information for coordinating research activities (recruitment outcome, research interview call log and interview visit schedule, etc.) will be password protected and kept on the secure FSM network drive. Only the PI, project manager, and RAs will have access this database. Identifiers included in the database include: name, MRN, address, phone number, DOB. Upon completion of all study-related data collection the Access database will be deleted.

Study generated data will be stored within REDCap and SharePoint and will be downloaded (void of all identifiers) into the project's Analytic folder on the FSM server. Upon completion of the study, a final dataset, void of all identifiers will be created, and stored indefinitely for secondary analyses.

25.0 Provisions to Protect the Privacy Interests of Subjects

25.1 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). All study generated datasets will be stored on the FSM server. In order to preserve participants' confidentiality rights, research subjects 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 participants. All electronic data will be stored in on a password-protected computer. A master study tracking database will be created using Microsoft Access and will be separate from all study responses that are collected in REDCap. This database will be encrypted and password protected, kept on a secure server and only accessible by study personnel. Survey data will be stored in a REDCap. EHR extraction data will be stored in SharePoint. The data will not contain any identifiable information. Individual study identification numbers will be assigned to each participant and only this number will appear on the survey. Only information that has been generalized and/or de-identified will be shared.

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 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 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 interview and discussion group will mitigate any risks associated with expressing their opinions (e.g., feeling uncomfortable).

25.3 All enrolled participants will provide written, online, or verbalconsent, include HIPAA authorization for the collection of all data, including review of the patient's medical records.

26.0 Compensation for Research-Related Injury

N/A

27.0 Economic Burden to Subjects

N/A

28.0 Consent Process

28.1 Written consent will be obtained for all participants, prior to their participation. The consent process will take place in a private room at NMHC, Northwestern Medicine Regional Medical Group clinic, in community sites in the participant's neighborhood

(i.e. private study rooms in libraries) or IMA clinic. We will follow "SOP: Informed Consent Process for Research (HRP-090)." For patients unable to complete the in-person interview/in-person written consent due to COVID-19 in-person interview restrictions, we will complete an online consent with HIPPA authorization and complete the baseline by phone after consent is obtained. The RC will send patients a link to Redcap either by email or SMS text to be able to read through the consent with the RC following the protocol below. If the patient agrees to participate, they will be asked to sign and date the online consent.

If a patient is unable to complete an in-person written consent or online consent due to inability to use technology for online consent, we request a waiver of documentation of informed consent and an alteration to obtain verbal HIPPA Authorization. Due to restrictions to in-person interviews during the COVID-19 pandemic, in-person interviews will not be able to be completed in-person to protect patients' safety and to follow Northwestern guidelines. For patients that are unable to complete online consent or written consent, research cannot practicably be conducted without the waiver or alteration. After verbal consent and HIPPA Authorization is obtained, the consent date and the name of the research coordinator that obtained the consent will be recorded in Redcap by the RC prior to starting the baseline interview.

Informed, online and verbal consent will be viewed as a process, i.e. at several times during review of the IRB approved consent document, the subject will be asked to explain in his/her own words what 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 that he/she is free to withdraw at any time without penalty. Information will be provided to the subjects in terms that they can fully understand. There will be no exertion of any overt or covert coercion. They will be encouraged to ask questions prior to giving consent.

Providers. We will ask providers to consent to be part of the study, which includes consenting to be randomized to one of the three 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. Thus they will be asked to sign a written or online consent to be a part of the study, which includes their consent to allow their patients to be randomized to condition, as well as their willingness to allow us to contact them for feedback via survey.

Patients. Subjects will be informed about the nature of the study by a CITI certified RA and asked to provide consent. Specifically, they will be told that depending on the doctor they see, they may be given additional educational materials and tools to help them better understand their medication. They will also be told that their physician may provide them with additional education. Additionally they will be notified that only those contents of their medical record that are necessary to evaluate the effectiveness of the intervention will be released to the research team at

Northwestern. Finally, they will be informed about the follow-up visits for the study, including 2 visits (at 3 and 6 months). They will be informed that they may withdraw from the study at any time and given contact information for the PI and study coordinator. For in-person interviews, the patients will complete a written informed consent document and will be given a copy of the consent document. See consent document. For phone interviews, the patient will complete an online consent or verbal consent and verbal HIPPA Authorization. For online consents, patients will be informed they can print their screen to keep a copy of the consent. For patients that complete a verbal consent, they will be emailed or mailed a blank copy of the consent document for their records.

Non-consenting patients. Subjects in this study are consenting to follow-up; however, because of the nature of implementing the EHR-based intervention at the system level, it is possible that patients who are seen after hours (outside of RA availability) will receive the EHR components of the intervention without being approached for consent or enrolled in the study. Note that any patient not enrolled in the study and not providing written consent will not be called to ask to participate in follow-up visits. We believe that were a patient to see an enrolled physician and thus potentially receive the EHR-components of the intervention, that the patient would not be exposed to any additional risk as the physician-facing interventions (e.g. EHR alert) are educational and do not change the prescribing practices of the physician.

Changes to the care delivery as a result of the intervention should be perceived as an exploratory quality improvement activity, and therefore reasonable that some patients may be exposed to new, available services as part of the study.

Follow-up providers. The physicians enrolled will be asked to consent to complete a survey gauging their responses to the intervention which their patients received. These providers will be asked to document their consent by clicking an "I agree" box (on the electronic version of the survey) or by returning the survey (paper version of the survey).

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

28.3 Verbal consent process for COVID-19 survey: Subjects will be informed about the nature of the study by a CITI-certified RC and asked to provide verbal consent. They will be informed that they may withdraw from the study at any time and given contact information for the PI and RC. A verbal consent, or a waiver of documentation of consent, is deemed appropriate because the nature of the study involves minimal risk and no PHI will be collected. If a patient agrees to participate after the RC reads the consent, the RC will record the patient's name on the consent form and the RC 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 if they request it.

For the follow-up waves of the COVID-19 survey, the same verbal consent process will be followed as above prior to wave 2.

28.4 Online and verbal consent process for COVID-19 Waves 5-9: Subjects will be informed about the nature of the study by a CITI-certified RC and asked to provide online consent with HIPPA authorization and complete the wave 5 interview after consent is obtained. If interested, the RC will send patients a link to Redcap either by email or SMS text to be able to read through the consent with the RC following the protocol below. If the patient agrees to participate, they will be asked to enter their first and last name, signature, date of birth, and date of consent to complete the online consent.

If a patient is unable to complete the online consent due to inability to use technology for online consent, we request a waiver of documentation of informed consent and an alteration to obtain verbal HIPPA Authorization. After verbal consent and HIPPA Authorization is obtained, the consent date and the name of the research coordinator that obtained the consent will be recorded in Redcap by the RC prior to starting the first phone interview.

Informed, online and verbal consent will be viewed as a process, i.e. at several times during review of the IRB approved consent document, the subject will be asked to explain in his/her own words what 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 that he/she is free to withdraw at any time without penalty. Information will be provided to the subjects in terms that they can fully understand. There will be no exertion of any overt or covert coercion. They will be encouraged to ask questions prior to giving consent.

Once online consents are filled out, they will get an automatic email with the signed version of the consent. Patients will also be informed that they may print their screen to keep a copy of the consent. For patients that complete a verbal consent, they will be offered a copy of the consent document to be sent via email or mail for their records according to their preference.

29.0 Process to Document Consent in Writing

29.1 All procedures listed in "SOP: Informed Consent Process for Research (HRP-090)" will be followed.

29.2 Providers being randomized to study arms
Written informed consent or online consent will be obtained from physicians (both attending and resident physicians). All participants 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 EHR-based intervention will be kept confidential and made anonymous in reports. If the physician does not want to participate or decides to stop before completing the patient enrollment period, this will not be disclosed to any superiors.

Patients
Stratified by clinic, randomization occurs at the physician level, where patients are randomized to the same group as their physician. Therefore patients will be recruited for follow-up purposes only, rather than for consent to the EHR portion of the intervention. For patients consenting to follow-up, the consent will be documented in writing.

For those patients receiving the intervention on the basis of having a consented provider, but not approached or consented for follow-up, we request a *waiver of informed consent* because: 1) this is a low-risk study, in particular, it is research designed to evaluate an educational strategy, 2) it would not be feasible to conduct the study as intended if obtaining individual informed consent were necessary (in this case because patients do not become eligible until a prescription is written for a new or changed medicine - but a key component of the intervention is the text on the prescription), 3) informed consent from each participant would threaten the scientific validity of the study (in this case it would be impossible to evaluate real-world dissemination and implementation of the intervention if the EHR automations needed to be turned on and off at the individual patient level) and 4) for the patients receiving the intervention, but not completing follow-up, no patient data are collected that would not be routinely collected in usual care without consent.

As detailed above, 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).

Follow-up providers. Follow-up providers will document their consent to completing the survey as detailed above: by clicking an "I agree" button (electronic version of survey) or returning the survey (paper version of the survey).

30.0 Drugs or Devices

N/A