PROTOCOL TITLE:

EHR-Based Medication Complete Communication (EMC^2) Strategy to Promote Safe Opioid Use: A Physician Randomized Trial

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1.0 Objectives

1.1 The overall objectives of the research grant are listed below; patients and providers will be involved in the data collection for Aims 1 & 2 whereas Aim 3 & 4 will not have any patient involvement and will assess costs of implementation from a system standpoint and plans for dissemination:

Aim 1: Test the effectiveness of an EHR-based Medication Complete Communication (EMC^2) strategy, with and without SMS text reminders to improve patient understanding and use of opioid medications.

Aim 2: Evaluate the fidelity of the EMC^2 Strategies and explore patient, provider, and health system barriers to the implementation and effectiveness of either intervention.

Aim 3: Assess the costs required to deliver the interventions, exclusive of system design.

Aim 4: Develop a dissemination plan for the EMC^2, with any necessary modifications, to other emergency departments and relevant medical practices.

1.2 Related to Aim 1 above, we hypothesize that leveraging an electronic health record (EHR) based Medication Complete Communication (EMC^2) strategy will reduce medication errors with newly prescribed opioid medications demonstrated by patient use compared to usual care. Compared to those receiving usual care, patients receiving the EMC2 strategies will:

H1 Report higher rates of provider (physician and pharmacist) counseling
H2 Have a greater understanding of risks associated with newly prescribed opioid medications
H3 demonstrate more appropriate safe use of prescribed high-risk opioid medications

2.0 Background

2.1 Research has repeatedly demonstrated that individuals lack essential information on how to safely take medication they are prescribed.[1-6] Knowledge deficits are greatest for information pertaining to risks and warnings.[7] This general lack of awareness is a leading root cause of the many cases of misuse that have translated to serious adverse events.

2.2 Neither physicians nor pharmacists routinely counsel patients to ensure understanding, leaving patients to rely on product labeling, such as the package insert, container label, or medication

leaflets.[8-12] These existing tools that have been designed to inform individuals on the safe, appropriate use of a prescribed(R_x) medication - including risks and warnings – are limited in their effectiveness. Even when evidence-based practices are employed to develop these written communications, those with limited literacy and numeracy skills - and older adults - may remain at greater risk for poor understanding and medication errors.[13-15]

Poor understanding of medication risks is particularly concerning for opioid pain relievers. In the past decade, there has been a marked increase of opioid prescriptions and a corresponding increase in the number of deaths from both opioid abuse and unintentional misuse.[16-20] In 2008, opioid pain relievers were involved in 74% of all deaths from prescription drug overdose.[16] Widely variable and often inadequate patient counseling about this class of medications may contribute to this, especially in the Emergency Department (ED) where pain is the most common complaint and opioid pain relievers the most commonly prescribed medication.[21-26] 39% of all opioids are prescribed in the ED, yet both spoken and written counseling is minimal.[27-29]

At the national level, the Food and Drug Administration (FDA) and Drug Enforcement Agency (DEA) endorse health system interventions targeting long-acting and extended release opioids and have focused many efforts on the physician prescriber.17,30 To date, the ED response has also been to focus on the prescriber by trying to reduce inappropriate opioid prescribing.31-36 Yet interventions are also needed to improve the prevalence and quality of patient education and counseling at the time of appropriate prescribing.

2.3 With the increasing adoption of EHRs and mobile technologies, we now have the ability to impart risk information to individuals at multiple time points and via multiple modalities. We will implement an EHR-based, Medication Complete Communication (EMC2) strategy, wherein 1) emergency physicians adequately counsel patients at the time of prescribing, 2) tangible tools reinforce counseling, and 3) a mechanism for follow-up engages additional providers to reinforce education and confirm understanding.

3.0 Inclusion and Exclusion Criteria

3.1 **Screening for eligibility for study**

Emergency Department Providers. The research study will be described to providers by the emergency department leadership and study leadership, both via email and at in-person business meetings. All ED providers

(attending MD, resident MD, NP, PA) with the exception of study investigators will be eligible. Providers will be asked to complete a written consent form if they choose to be involved in the study.

Patients. During the patient recruitment period, the RA will make frequent rounds through the ED and ask physicians to identify potentially eligible patients who will be discharged home on opioid pain relievers. The RA also will carry a pager so that physicians can notify the RA if they have an eligible patient. This method of patient identification has a well-established track record within our ED for maximizing enrollment while minimizing RA downtime. If the patient is interested in participating or learning more about the study, the RA will obtain verbal permission to ask the patient a brief series of questions to determine eligibility (see criteria below). If the patient is eligible for the study, the RA will proceed with obtaining written informed consent.

Follow-up Providers. Certain providers will interact with consented patients after the intervention takes place (e.g. Primary care physicians (PCP) and outpatient pharmacists). These providers will have no required role in carrying out the intervention (which is carried out by the EHR enhancements). These providers will be identified by chart review (PCP) and pill bottle review (pharmacists) at the time of patient follow-up. <30% of ED patients have on-staff PCP and there is no way to predict where the patients will fill their prescriptions (e.g., on-site Walgreens or another pharmacy). After identifying these providers at the time of follow-up, we will contact them via email or mail to participate in a survey. Both types of surveys will be offered to accommodate providers' busy schedules and because the pharmacists are located at diverse locations across the across the city of Chicago. The survey will assess the implementation of the EHR interventions and the providers' reactions to receiving additional information about their patients who were prescribed opioids in the ED.

3.2 **ED Provider Inclusion Criteria.** 1) Resident, Attending Physician or Mid-level provider (NP, PA) working in the Northwestern Emergency Department during study dates.

ED Provider Exclusion Criteria. 1) Study investigator.

Patient Inclusion Criteria. To be eligible to enroll and remain in the study, patient subjects must meet all of the following criteria: 1) Patient age 18 years and older, 2) English language speaking 3) prescribed pill form of hydrocodone-acetaminophen opioid pain reliever 4) the patient is the person primarily responsible for administering medication

Patient Exclusion criteria. Subjects will be excluded from the study if any of the following conditions are met: 1) Aged <18, 2) non-English

speaking, 3) clinically unstable, psychologically impaired or intoxicated as judged by research staff member or emergency physician, 4) chronic opioid use, defined as daily or near daily use of opioid pain relievers for the past 90 days 5) admitted to hospital 6) unable to complete follow up phone interviews 7) pregnant

Follow-up Provider Inclusion Criteria: 1) Primary care physician within Northwestern system who has seen patient enrolled in study as part of routine ED follow-up or 2) Pharmacist who filled opioid prescriptions for study participant.

Follow-up Provider Exclusion Criteria: none

3.3 **Special Populations**
No special or vulnerable populations will be included.

4.0 Study-Wide Number of Subjects

4.1 Number of Emergency Department Physicians and Mid-Level providers to be enrolled. N=150
Number of Patients to be Enrolled. N=1500
Number of follow up providers to be enrolled (PCP/Pharmacists) N=50

5.0 Study-Wide Recruitment Methods

N/A

6.0 Multi-Site Research

N/A

7.0 Study Timelines

An individual ED physician or mid-level provider will be involved in this study for a maximum of two years of patient enrollment.

An individual patient subject will be involved in the study for a total of 1 month. They will complete a baseline enrollment interview, a phone interview at 2-4 days, a phone interview at 7-14 days, and a final phone interview at 1 month.

An individual PCP or pharmacist will be involved in the study for the amount of time it takes to complete the survey questionnaire (estimated at approx. 5-10 minutes).

We anticipate that patient enrollment will actively take place for 1.5 years to reach the target N above; however if accrual occurs at a slower rate we have allowed 2 years. The estimated date to complete primary analyses is May 2017.

8.0 Study Endpoints

8.1 Covariates. Baseline assessment will include a sociodemographic and health questionnaire and questions about previous use of opioids. A literacy assessment using the Newest Vital Sign (NVS) will be performed.

Primary Endpoint. Demonstrated understanding of how to properly dose the opioid medication as measured by participants' ability to correctly dose their prescription regimen using a demonstrated dosing exercise previously used in studies by both Drs. McCarthy and Wolf. Primary endpoint will be assessed at the 7-14 day phone interview.

Secondary Endpoint. Actual use of the opioid medication as measured through the review of the medication diary, participant report of refills and new opioid prescriptions received patient opinion of the intervention as measured by both closed and open-ended questions at the time of follow-up phone interview; patient risky-behaviors while on opioids, as measured by patient self-report. Other aspects of safe use related to *risk awareness* will be assessed using a questionnaire, as will beliefs about medication use. The questionnaire will assess topics including safe storage of opioids, sharing of opioids, disposal on completion of the prescription, and questions related to possible dangerous behaviors. Secondary endpoints will be assessed with phone interviews .

Tertiary Endpoints. The identification of medication names, dosage, risks, warnings, and benefits will be assessed through a structured questionnaire that has been developed and used extensively by Dr. Wolf and colleagues in multiple studies and current NIH-funded grants. The self-report of provider counseling will also be measured. Tertiary endpoint assessments will be assessed via phone interviews.

Exploratory Endpoint. A subset of analyses will examine return visits to the ED (obtained via EDW query) and admission to the hospital for a complaint related to opioid pain reliever (ranging from mild, e.g., constipation to severe, e.g., respiratory depression). Additional analyses will be conducted to evaluate for possible misuse or inappropriate prescribing. Outcome indicators include: 1) opioid overlap (defined as opioid prescriptions that overlap by 7 or more days, including refills), 2) opioid and benzodiazepine overlap, 3) long acting/extended release opioid prescription written for acutely painful conditions 4) high daily opioid dosage (defined as a prescribed daily dose of 100 morphine milligram equivalents (MME) or greater) and 5) opioid dose escalation (measured as having a 50% or greater increase in mean MME per month twice during the year).[91,92] These data will be obtained by a data pull via the Illinois

Prescription Monitoring Program (ILPMP) at 1-year post initial ED prescription. Drs. McCarthy and Lank will conduct this data-pull. Patients PHI will not be sent to the ILPMP or any other state or pharmacy governing body to obtain these data.

9.0 Procedures Involved

9.1 We will conduct a three arm physician randomized study trial in the emergency department at Northwestern to measure the effect of an EHR-based, Medication Complete Communication (EMC^2) and EMC^2+SMS text reminder strategies on increasing provider counseling, increasing patient understanding of risks associated with newly prescribed opioid medications, and demonstrating more appropriate, safe use of prescribed high-risk opioid medications. English speaking patients who are prescribed hydrocodone-acetaminophen will be recruited and assessed with phone interviews at 2-4 days, 7-14 days and 1 month.

9.2 Provider Randomization. To optimize the likelihood of obtaining similar populations in each intervention arm, providers that have consented to participation in the study will be placed into 4 strata depending on their role (attending versus resident) and historical volume of opioids prescribed. Dr. Kim, blinded to provider identity will randomly assign providers within each stratum to each of three study arms using a random number generator. We will reveal provider identities after randomization is complete.

Provider role and training. All providers will be informed of the possible interventions that their patients may receive (e.g., Universal Medication Schedule sig codes (See below on page 9), Medication Sheet, Text reminders, and emails to PCP as well as any changes such randomization may cause to the providers workflow (i.e, for some providers, intermittent pop-ups reminding them to counsel patients). Providers will be told that they will be assigned to either the usual care or one of two intervention groups. The providers who are assigned to the intervention groups will be trained on how to 1) prescribe medications with the EMS instructions from the "favorites" list and 2) how the other components of the intervention will automatically generate (MedSheet, emessage to PCP).

The initial study visit (baseline) will be conducted at the time of patient enrollment. Following this baseline interview, RAs will conduct three telephone interviews (at 2-4 days post-baseline, 7-14 days post-baseline and at one month post-baseline). The first two assessments (at enrollment and 2-4day follow-up call) have been included to closely track patient recall of counseling and knowledge, while the latter two assessments (7-14 day follow-up call and 1 month follow-up call) are included to assess decay of knowledge, safe use, storage of medications and demonstrated dosing. The final call (one month post-baseline) will assess disposal of

medications and determine if patients have received additional opioid pain relievers from other providers.

Baseline Interview. At the time of enrollment, the RA will ask the participant to indicate the best days and times to call within a 2-4 day range. A $5 Gift card given to the participant for completion of enrollment tasks.

First Study (2-4 Day) Phone Call. The study phone call will be conducted at a time of convenience for the patient, however still within a 2-4 day range post-baseline. Additionally during this phone call, the RA will either confirm or schedule the 7-14 day follow-up call. A $10 Gift card will be mailed to the participant for completion of first phone call.

Second Study (7-14 Day) Phone Call . The second phone call will be conducted at a time of convenience for the patient, however still within 7-14 day range post-baseline. Patients will be compensated for their time to complete the call with a$20 gift card which will be mailed to the participant upon completing the call. Patients will also be asked to mail back their de-identified medication diary using the prepaid envelope provided at baseline.

Third/Final Study (1 Month) Phone Call. The final study phone call will be conducted at a time of convenience for the patient, however still within 1-month post-baseline. (See Attached Interview script)

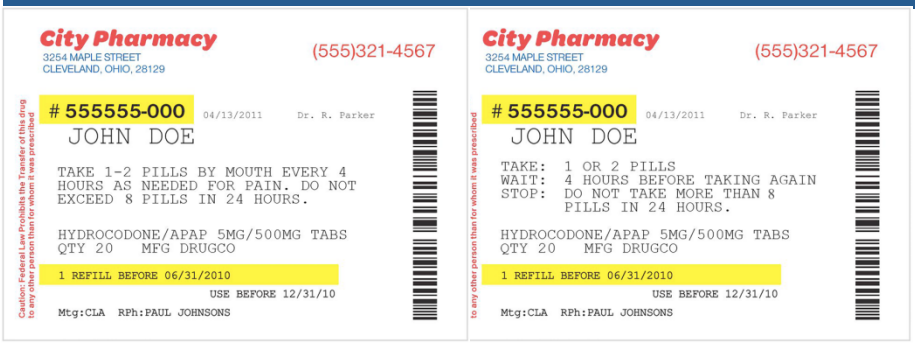
Intervention Patients with physicians randomized to the EMC^2 arm will receive the 5-part EMC2 intervention.

[1] Funded by AHRQ [R18HS17220], we created single-page, plain language medication information sheets with content appropriately sequenced from a patient's perspective (drug name, indication, purpose/benefit, how to take, for how long, when to call your doctor, when to stop taking and call your doctor, important information) and following other health literacy best practices.

[2] The medication sig ('sig' is short for *signa*, which in Latin means "write") contains directions to the patient (e.g.: "take one pill every 8 hours). We have shown that we are able to replace existing EHR default sigs for the top 300 medicines prescribed in primary care with UMS instructions [R21CA132771] and have evaluated the use of UMS sigs in actual pharmacy practice [R01HS017687] for non-PRN medications. The UMS sig for PRN medications has been evaluated in two studies (California Healthcare Foundation, McNeil Consumer Healthcare), and we have found that patients with the UMS sig for PRN dosing (Take-Wait-Stop label) were less likely to exceed the maximum daily recommended

dose of their opioid prescription. The UMS Sig for the opioids in question in this study will change the text on the prescription bottle as demonstrated in Figure 1

Figure 1: Standard label (left), UMS Take-Wait-Stop label (right)



[3] In addition to the tools that the patient receives, the EHR will automate communication to the patient's prescribing ED physician, reminding them to counsel the patient with a pop-up window.

[4] Additionally, there will be communication to the dispensing pharmacist by making a note on the paper-prescription requesting the pharmacist consider counseling the patient.

[5] Finally, there will be a notification to the primary care physician (PCP) if the patient has a PCP in the Northwestern system. This notification was initially conceptualized as being automated when the inpatient and outpatient Cerner systems were compatible. Since the switch of the outpatient Northwestern Medicine offices to the EPIC EHR, this automated function is not longer available. Therefore, the RAs enrolling the subjects will note if the patient has a Northwestern Medicine physician. If the patient enrolled for follow-up has a physician in the system, the RA will manually log-in to the outpatient EPIC interface (with write functionality) and send the PCP an inbox message with the following sample text: "Your patient NAME, DOB was seen in the Northwestern Emergency Department on MONTH DATE, 20XX. They received a prescription for Hydrocodone-Acetaminophen (DOSE, TIMING, NUMBER OF TABS). When you see this patient for a follow-up appointment, please consider counseling them about the safe use of this medication. For additional information about your patient's visit to the Emergency Department, you may access the Emergency Department Note and Depart Summary. The Depart Summary will also contain a copy of the information sheet that your patient received about their new prescription pain medication."

[Note: Neither the Pharmacist nor the PCP receiving the messages to "consider counseling the patient" are required to take any action as part of the intervention. The study is designed with the ED as point of care and we will be assessing implementation to gauge the response to these messages among those PCPs and pharmacist who received them; however, these providers are not required to do anything as part of the study or intervention.]

Patients with ED physicians randomized to the EMC2 +SMS Text reminder arm will receive the above-described 5 components of the EMC2 intervention, and also will receive daily text reminders for one week (7 messages) following the new prescription for an opioid pain reliever (only consented patients). The premise for the 1-week timeframe is to help patients remember precautions regarding safe use during the time they are taking the medication (average ED R_x for opioids is from pilot data is 18 tabs). Furthermore, SMS text reminders that would continue indefinitely are at risk for either being ignored, irritating patients, and/or adding an unnecessary expense to patients (i.e., patient does not have an unlimited texting plan, further challenging sustainability). Messages sent early in the week will focus on topics such as safe storage and use; those sent near the end of the week will focus on topics such as disposal and pill sharing. We will schedule EMC^2 text messages to arrive mid-day (12:00pm to 5:00pm), based on patient preference. (See appendix for sample text messages)

9.3 Procedures to monitor safety and minimize risk.

As a part of all of the time points of follow-up, the RAs will have a checklist of potentially dangerous behaviors related to opioids and if these items are noted in the course of data collection the RAs have a set protocol to follow. (see safety protocol attached)

9.4 The drug hydrocodone-acetaminophen is the topic of the research; however it is not being used in the research—the intervention is focused on education about this medication and the study will not change the drug, dose, frequency, quantity or refills that the ED physician selects in the course of their normal clinical care.

Sources of Materials:

Electronic Health Record (EHR): Patient information and outcomes will be extracted from the EHR (demographics, ED return visits and re-admissions). Re-admissions and re-visits to the hospital and ED data will be abstracted from medical records for all patients enrolled into the study, as well as all patients prescribed an opioid during the recruitment period of 18-months.

Illinois Prescription Monitoring Program (ILPMP): We will obtain data from the ILPMP on medication fill date, subsequent refills of the prescribed opioid, and new prescriptions for other controlled substances.

All personal health information will be kept behind organizations' firewalls. Analytic databases will be created with removal of all personal health information; these will then be sent to Northwestern investigators for analysis.

Patient in-person enrollment & follow-up phone interviews: Interviews include assessments of health literacy skills, safe medication use, and medication understanding, among others.

Provider surveys: Both the ED providers and the follow-up providers (PCP and Pharmacists) will be surveyed to assess their reactions to the intervention via electronic and mail survey.

10.0 Data and Specimen Banking

10.1 Data will be stored for up to 5 years after study completion for data analysis and publication of study results. At that time, all identifiers will be destroyed, but de-identified data will be retained. Data will be stored on Northwestern encrypted servers and access will be granted through the PI.

10.2 The clinical data, interview data and prescription refill data noted above will be stored.

10.3 Data will not be released.

11.0 Data and Specimen Management

11.1 AIM 1 Analysis Plan. The proposed trial uses a cluster-randomized design where the prescribing physician is the unit of randomization. We will randomize approximately 150 physicians (50 attending physicians, 100 EM resident physicians and mid-level providers) to three intervention arms (usual care, EMC^2, and EMC^2 + SMS text reminders). The estimate of 150 includes a base of 100 providers with an estimate of approximately 50 new providers over the course of the 18 months of recruitment (e.g. 15 new residents in 2015, 15 new residents in 2016 and new attending hires). At any given time, we estimate that 100 providers will be actively involved in the study, resulting in approximately 33-34 physicians per arm. Physicians will be stratified by provider role (i.e., attending vs. resident) and randomly assigned to one of the three arms with an equal number assigned to each. We will accrue approximately 12 patients per physician; we conservatively anticipate at least 54% retention for the phone call follow-up 7-14 days post prescription. These estimates will result in 1500 participants recruited with an anticipated

minimum of 816 patients at in-person follow-up (272 per arm, 8 per physician) available for primary data analysis.

To ensure adequate balance across the 3 arms, potential confounders including socio-demographic characteristics, comorbidities, regimen complexity (i.e., # of medications, total pills taken daily), health literacy level, and history of opioid use) will be compared using one-way ANOVA models and χ^2 tests, as appropriate. Covariates with significant differences (p-value < .05) across treatment groups will be included in the generalized linear mixed models (GLMMs) to adjust for the group differences as described below. We note that detected differences may be physician-specific, so if we observe differences across the treatment arms, we will explore whether the difference might be attributable to individual physicians.

Demonstrated safe use by not exceeding the maximum dose is the primary outcome of interest for Aim 1 (H_3), with higher reported rates of provider counseling and greater understanding of risks relevant to hypotheses of secondary interest for Aim 1 (H_1, H_2). We will use GLMMs for analyses of the data, specifying the logit link function for the binary outcomes using xtmixed in Stata (v.12.1). The 3-category treatment group variable will be the independent variable of primary interest and modeled as a fixed effect with the usual care group specified as the reference. We will also include fixed effects for any potential confounding covariates noted in the descriptive studies that were not accounted for in randomization. Random effects will be included for each physician to account for intra-physician correlation among participants. For all GLMM analyses we will report point estimates and corresponding 95% confidence intervals. We will examine and report the extent to which the random effects suggest correlation of outcomes within physicians.

Measures taken to minimize bias. For the randomization scheme of this study, physician is the unit of randomization rather than patient. With healthcare interventions and quality improvement projects, such as the one proposed herein, there are no other ways to evaluate an automated EHR process than to "turn them on." This is why the randomization will occur at the physician level rather than the patient level. This process will result in trickle down of aspects of the EMC^2 intervention (but not SMS texting) to patients seen by the consented provider, but not enrolled in the study for follow-up purposes (e.g., on overnight shifts).

Level of significance to be used. We will use a two-sided 5% significance test

Stopping rules. We will stop enrollment once we have reached the 1500 patient enrolled maximum.

Procedures for reporting deviations from the original plan. Any deviations involving human subjects will be submitted to the IRB for review before being implemented.

Selection of subjects for inclusion in the analysis. All subjects with complete information (e.g., at least 80% completion of interview instrument) will be used in the analysis.

AIM 2 Analysis Plan. Following completion of enrollment, we will determine the extent to which the interventions were implemented as planned (a process evaluation) in the two intervention arms. In the EMC^2 and EMC^2 + SMS text reminder arms, we will collect EHR data on prescriptions and discharge summaries to assess if patients actually received the new prescriptions with the UMS (Take-Wait-Stop) sig, and review pill bottle information during the 7-14 day phone call to determine if the sigs were translated accordingly onto patients' drug labels. For the EMC^2 + SMS text reminder arm, we will ask patients at all follow-up intervals if they received the text messages. For those electing to turn off the service, we will qualitatively explore and code reasons why.

Usability of the EHR interventions will be assessed among the ED physicians and follow-up providers (PCPs and pharmacists) via survey.

AIM 3 Analysis Plan. We will directly measure and assess the provider perspective costs of running the two EMC^2 interventions. Specifically, we will estimate the incremental cost of the interventions relative to usual care from the perspective of the ED implementing these systems. The primary costs of running the EMC^2 intervention involve the limited expenses around printing (printer ink, paper, staff time). However, we will include estimates for minimal programming maintenance and will test the sensitivity of results to changes in the maintenance requirements in terms of programmer hours. We also will separately track development costs for software and other programming requirements based on programmer hours. The greater cost, in terms of running the program, will be that for the SMS text services, which will include the nominal monthly cost as well as staff time to schedule the SMS text reminders after the initial ED visits. For study purposes, the RA will do this task; however, we will have record on a daily basis in a study database (Microsoft Office Access, Microsoft Corp.) the number of minutes spent programming the SMS text reminders. This record will allow us to estimate the direct staff costs of this component by combining time with wage estimates. We will test the sensitivity of costs to different assumptions about the potential use of variable staff (nurse, clerk, medical assistant) using different salaries but assuming the same proficiency in terms of time required. Further we will assess the sensitivity of the

estimates to different proficiency levels that could arise from learning by doing.

To achieve Aim 3, Surrey Walton, at UIC, will help in analyzing time and resource use related to the intervention. Any data that he would receive would be anonymous and would not contain any patient PHI. Instead, the data would involve counts of hours spent, and materials used, in creating and implementing the intervention.

11.2 Rationale for choice of sample size, power considerations. The sample size for this study was based on pairwise comparisons between the two intervention arms compared to usual care (i.e., usual care vs. EMC^2 and usual care vs. EMC^2 + SMS). This calculation was based on the primary outcome of demonstrating safe use by not exceeding the maximum recommended dose at the 7-14 day phone follow-up interview.

Conservatively estimating 54% retention rate for 7-14 day follow-up call, we will have 82% to detect a difference of 11.8% between each intervention and the usual care arm assuming a Type I error of 2.5% to account for the two comparisons. An intraclass correlation coefficient (ICC) of 0.001 was used because we do not expect patient outcomes to be influenced by the clustering of physicians due to patients being randomly assigned a physician upon ED entrance and physicians typically working a random assortment of shifts.

With the sample size set by the primary outcome of demonstrated safe use by not exceeding the maximum dose, we also show detectable effects for the secondary outcomes in Table 3, assuming at least 80% power, a Type 1 error rate of 2.5%, an ICC of 0.001, and usual care estimates from prior studies.

11.3 Data Safeguarding Procedures. Any information that could allow identification of individual patients, including the master list, will be kept strictly confidential. In order to preserve participants' confidentiality rights, research subjects will be assigned study ID numbers that will be used to identify all the information collected. A master study tracking database will contain information linking participants to their study ID numbers. This database will be on RedCap and is both encrypted and password protected and only accessible by approved study personnel at Northwestern. Grant file access permissions will only be given to specific approved research personnel, as designated by the PI.

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

Data Safety and Monitoring Board. The Data Safety and Monitoring Board (DSMB) will be formed in the early months of the project and be given responsibility to review and approve the study methods and analysis plan for all research aims. The DSMB members will be recruited by Dr. McCarthy and will include 4 local health services researchers, methodologists, and biostatisticians with related expertise. DSMB members will meet in person once a year. At these meetings the study protocol, procedures, and any issues of concern related to research integrity will be discussed. Additional meetings may be arranged for late-breaking issues. (See **Appendix** for DSMB protocol)

Adverse event monitoring. This is a behavioral interventional study. No individual administration of any therapeutic or prophylactic agent is required in this protocol and there are no procedures required by the protocol. However, because this study does involve interview questions related to the use of a medication, namely hydrocodone/acetaminophen, safety measures will be in place to detect any unsafe medication use by the patients at home. These adverse events may occur during the course of the study period from overdose (whether accidental of intentional), from abuse, from concomitant use with other products (sedatives or acetaminophen) and from withdrawal. The research assistants conducting the phone interviews and completing review of the medication diaries will have a protocol in place to identify any concerning medication use patterns with an action plan outlined if events are detected. (See attachment)

It is the expectation of the investigator that because this study is a non-invasive behavioral intervention that most, if not all, adverse events are unlikely or definitely not related to study participation or the intervention. These adverse events will be reported annually as part of regular data reporting. If any adverse events are serious or potentially study related, they would be reported as required in the time period required by the IRB.

13.0 Withdrawal of Subjects

13.1 In the case that subjects do not complete their follow-up phone interviews and do not respond to 3 calls attempting to re-schedule, they will be withdrawn from the study. Additionally, if subjects exhibit inappropriate or violent behavior towards research personnel, they will be withdrawn from the study.

13.2 If a subject decides to withdraw from the study, there will be instructions in the consent document (all patients provided signed copy) with information regarding contacting the study coordinator or PI to withdraw their consent.

13.3 If a subject withdraws from the study the data collected to that time point will be retained to assess for bias in the final sample. They will not be contacted further for interviews.

14.0 Risks to Subjects

14.1 Patients who receive care at the participating Emergency Department during this study will be subject to minimal risk through their participation. It is possible that subjects may feel shame and/or some emotional discomfort when taking the literacy and medication use assessments, and performing medication related tasks. We will also be making changes to how their medication instructions are written, and learning through follow-up interviews how they are implementing regimens. If we find that patients in any study arm are misusing medications, we will have a structure in place to address these concerns. This will be documented accordingly within internal study documents; however will not become a part of the medical record unless patients require acute care for their drug misuse or abuse. Consent forms will also acknowledge this disclosure.

Patients in one study arm will receive automated text messages that some could view as intrusive; however they will have the ability to opt-out of the messages at any time. With SMS texting via cell phones, only the phone number is entered into the automated texting system, and no other patient information. We will uphold patient confidentiality and respect any requests to turn off this function during the study.

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 number"), 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. 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 or clinic Institutional Review Boards will have the authority to review any study records. In such case, they too will be required to maintain confidentiality.

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 opioid 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 opioid use. Findings of the ED's ability to implement this intervention (and the cost associated) can help similar organizations improve patient education about the safe use of opioids in the future.

16.0 Vulnerable Populations

N/A

17.0 Community-Based Participatory Research

N/A

18.0 Sharing of Results with Subjects

18.1 No results will be shared with subjects. Patients' primary care providers may become aware that they are enrolled in a study through an EHR-notification, however this will not contain any study results—simply a note that the patient received a prescription for Norco and was counseled about it in the ED using the MedSheet.

19.0 Setting

19.1 Patients will be identified, consented and all procedures will be performed in either the Northwestern Emergency Department or over the phone with the participant.

20.0 Resources Available

20.1 The research team is comprised of has 5 PhD level researchers, 3 Physician-researchers (all of whom hold research masters degrees), a research-pharmacist, and a group of research assistants and statistical analysts (who have 2-10 years of experience working on similar projects). We have significant experience in recruiting patients from the emergency department, conducting studies related to medications (including the medication being studied), consenting patients to follow-up, and conducting multi-part follow-up with both in-person and telephone interviews. Additionally, the team has experience in managing data in accordance with the best-practices of the IRB to protect patients' confidentiality.

20.2 Initial estimates suggest that approximately 9,000 subjects will be potentially eligible for follow-up annually (representing 16% of discharged patients from the ED).

The PI has 30% protected time for this study throughout the study duration and full support of the Department of Emergency Medicine. The Co-Is have ample time supported to assist in weekly meetings, data analysis, DSMB review, and other study operational tasks. The three physician-researchers will be available at all hours for the RAs to contact if there are any concerns related to the safety protocol (see attached).

The study team will have 2 full-time RAs dedicated to enrolling and completing follow-up on the study with support from a team of other RAs to cover evening and weekend hours.

Facilities: The patients will be approached and consented for participation while in the Emergency Department. Follow-up calls by the RAs will occur at a time of convenience for the patient and the RAs have access to closed offices wherein to conduct the calls and record data.

All persons assisting in the project will be adequately informed about the research protocol, the research procedures, and their duties and functions. We will ensure this by conducting weekly research meetings (already in-place) and by reviewing key concepts and conducting practice sessions for the consent process and interviews.

21.0 Prior Approvals

21.1 We have received funding from the Agency for Healthcare Research and Quality.

22.0 Recruitment Methods

22.1 Patients will be recruited during daytime and evening hours in the Northwestern Emergency Department after being identified by the procedures outlined above in section 3.1.

22.2 Patients will be recruited in the Emergency Department at Northwestern.

22.3 During the patient recruitment period, the RA will make frequent rounds through the ED and ask physicians to identify potentially eligible patients who will be discharged home on opioid pain relievers. The RA also will carry a pager so that physicians can notify the RA if they have an eligible patient. This method of patient identification has a well-established track record within our ED for maximizing enrollment while minimizing RA downtime. If the patient is interested in participating or learning more about the study, the RA will obtain verbal permission to ask the patient a brief series of questions to determine eligibility (see criteria below). If the patient is eligible for the study, the RA will proceed with obtaining written informed consent.

22.4 The RA will explain the study to the patient. There are no advertisements.

22.5 Patients will receive a $5 gift card at the time of enrollment, $10 gift card will be mailed after completion of the 2-4 day phone call and

they will then receive a $20 gift card upon completion of the 7-14 day phone interview.

23.0 Local Number of Subjects

N/A

24.0 Confidentiality

24.1 Patients. After identifying eligible subjects, a member of the research staff will approach the patient and obtain written informed consent. Written consent will consist of permission to be contacted for the future phone interviews, permission for possible receiving additional information about their medication, and permission for medical record review. The research assistant will review the consent with participants. He/she will provide participants with information on the study plan and their rights as research participants. Participants' consent will be documented by their signatures. Subjects will be provided with a copy of the consent. They may withdraw at any time during the study without penalty or loss of any healthcare benefit or service to which they are entitled.

Patients who state that they do not want to receive further communication via SMS text-messaging will have the opportunity to cancel the text messages and not receive further outreach; they will be included in outcome assessments.

Data from the Illinois Prescription Monitoring Database will be obtained via individual patient record query for the enrolled patients. No protected health information will not be sent outside of Northwestern or to the State for a database query.

Patients will be assigned a unique identification number; The research database will be password protected and accessible only to the research team. Information linking subjects with their unique identifier will be kept on a separate password-protected desktop computer in a locked office within the Department of Emergency Medicine. We believe that in using these methods we will be compliant with the "Standards for Privacy of Individual Identifiable Health Information" under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule.

ED physicians, mid-level providers and follow-up providers
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.

25.0 Provisions to Protect the Privacy Interests of Subjects

25.1 Only patients consenting to participate in study follow-up will be asked to interact with study personnel at future dates (follow-up calls).

25.2 We will also attempt to reduce shame and performance anxiety as a result of interviews about compliance with screening and assessments through extensive training of the research assistants. If any misuse of the medication is discovered during the interviews, there will be a process in-place to connect them to further medical care if required (see appendix).

25.3 Stephanie Gravenor will conduct the EDW data pull to access the data elements from the medical record. The remainder of the RA staff will only access the chart if a patient had a return visit to the ED within 30 days of enrollment. In that case, a chart review of that visit will be performed by the RA. Two of the study co-Is will access the information in the Illinois Prescription Monitoring Database directly (Drs. McCarthy and Lank).

26.0 Compensation for Research-Related Injury

N/A

27.0 Economic Burden to Subjects

27.1 Patients in one study arm who receive text messages could have to pay at a maximum $0.70-$1.75 cents over the course of the project, assuming charges of 10-25 cents per text message received (depending on the cell phone company and receipt of 7 text messages). We believe this expense is justified because the intervention should aide in preventing misuse of the medication and the re-imbursement for study participation was created with this cost built-in.

28.0 Consent Process

28.1 ED 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 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 additional providers, including their primary physician and pharmacist, will be informed about their prescription and 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 components for the study, consisting of 3 phone calls (at 2-4 days, 7-14 days and 1 month). The patients will complete a written informed consent document and will be given a copy of the consent document. See consent document. They will be informed that they may withdraw from the study at any time and given contact information for the PI and study coordinator.

Non-consenting patients. Subjects in this study are consenting to follow-up; however, as mentioned above, 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 or phone calls. 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 of the ED 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. We will only examine data on outcomes that can be collected in aggregate and not from patient interviews (specifically, we will examine, via the EDW, return visits to the emergency department). There is no collection of PHI, rather a comparison of already available ED data between study arms.

Follow-up providers. The PCPs and pharmacists identified by chart review and pill bottle review during patient follow up 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). (See survey attachments with consent statements)

29.0 Process to Document Consent in Writing

29.1 ED physicians being randomized to study arms

Written informed consent will be obtained from ED 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 18-month patient enrollment period, this will not be disclosed to any superiors.

Patients

The intervention is implemented at the physician level. 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 an opioid—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. Specifically, the only data that will be accessed on this sample of patients is demographic data from the electronic medical record and data on return visits to the emergency department and re-admission to the hospital for problems related to pain and/or opioid use.

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

ATTACHMENTS:

a. Interview battery
b. Patient Consent
c. ED Provider Consent
d. ED Provider draft survey
e. Follow-up provider (PCP & pharmacist) draft survey
f. Safety Protocol
g. MedSheet (health literacy format)
h. Medication Diary
i. Sample Text Messages
j. DSMB Protocol
k. Appointment Reminder Card
l. Mini Mental Status Exam supplements