Cover Page

Study Title: PRescribing Interventions for Chronic pain using the Electronic Health record (PRINCE)

ClinicalTrials.gov #: NCT04601493

Study Protocol with Statistical Analysis Plan

Document date: May 9, 2022

Protocol Title	PRescribing INterventions for Chronic pain via the Electronic health record (PRINCE) study
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Scientific Assessment	Nationally-based, federal funding organizations
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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	July 29, 2020	Minor edits to web survey text, change in data storage plan for web survey data, per HIPCO	No
2	November 30, 2020	Edits to the plan for the PDMP data acquisition, storage, and analysis.	
3	December 8, 2020	Revised interim outcomes analysis plan approved by Data Monitoring Committee, and uploading the approved Data Monitoring Committee charter.	No
4	February 24, 2021	Including report from Data Monitoring Committee and changes to protocol to reflect those recommendations.	No
5	May 9, 2022	Minor changes to the analysis plan that were made before starting the actual data analysis	No

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ABBREVIATIONS/DEFINITIONS

- CDC: Centers for Disease Control and Prevention
- QI: Quality Improvement
- EHR: Electronic Health Record
- (1)ICS: Informatics Consulting Services
- MMB: Minnesota Management and Budget
- MME: Morphine Milligram Equivalent
- PCP: Primary Care Provider
- PDMP: prescription drug monitoring program
- PMP: Prescription Drug Monitoring Program
- MMB: Minnesota Management and Budget
- UMP: University of Minnesota Physicians
- DEA: Drug Enforcement Agency

1.0 Objectives

1.1 Purpose:

The objective of this research is to assess the effects of EHR-based decision support tools on primary care clinician decisionmaking around pain treatment and opioid prescribing. EHR-based clinical decision support tools are a common feature of QI The decision support tools are informed by principles of "behavioral economics," whereby clinicians are "nudged," though never forced, towards guideline-concordant care.

To test the effects of these decision support tools for improving the quality of care for pain treatment, we will implement a clinic-randomized QI study across the primary care clinics of Fairview Medical Group and University of Minnesota Physicians.

The study has two parallel components. The decision support tools to be tested will differ somewhat depending on whether a given patient is opioid-naïve, or whether a given patient is a current opioid-user. Four sets of analyses will be conducted separately: one for the opioid-naïve group using EHR data, one for the current opioid-user group using EHR data, one at the PCP-level using web survey data, and one at the PCP-level using MN Prescription Drug Monitoring Program data.

2.0 Background

2.1 Significance of Research Question/Purpose:

Three of the key dimensions to addressing the current opioid crisis are a) how to minimize the number of patients who are starting opioids and therefore at risk of developing dependence, b) ensuring that opioids that are prescribed are prescribed appropriately and safely, and c) how to effectively and safely reduce prescription opioid use among current users of prescription opioids.

Prior research establishes that behavioral economics-informed interventions that are embedded within the EHR can successfully improve clinicians' decisionmaking. For example, an influential paper by Meeker and colleagues (1), showed that EHR-based "nudges," similar to what we propose to test, successfully reduced rates of inappropriate antibiotic prescribing. A few studies use quasi-experimental methods to examine how changes in the EHR infrastructure affect opioid prescribing decisions, with mixed results.

As the opioid crisis continues, there is an urgent need to develop effective methods for improving pain treatment and opioid prescribing in primary care. Behavioral economics-informed interventions may be especially useful in the context of pain treatment and opioid prescribing. Specifically, decisions about opioid versus non-opioid treatments, monitoring opioid use, initial prescribing, and decisions around tapering and/or discontinuing opioids are idiosyncratic to the patient. Therefore, interventions which nudge towards treatment guidelines, without compelling any clinical action, may be especially promising.

We are proposing to implement a primary care clinic-randomized study of two sets of behavioral economics-informed interventions embedded in the EHR, to improve pain treatment and opioid prescribing decisions.

2.2 Preliminary Data:

We recruited five clinicians to pilot-test the interventions, and one additional PCP from the PRINCE study team (Dr. Elert) also pilot-tested the interventions. The pilot testers included a mix of three PCPs and three pain clinicians. The pilot-testing took place from 11/27/18 to 12/25/18. We received extensive feedback in the semi-structured exit interviews about how to improve the usability of the interventions, which informed the modifications we subsequently made to the interventions

2.3 Existing Literature: There is a recent and growing literature that studies how EHR-based "nudges" can affect clinician behavior around opioid prescribing and pain treatment. For example, two recent studies found that reducing the default number of pills per opioid prescription order within the EHR led to reduced amount of opioids prescribed after surgical procedures and at emergency department discharge (2, 3). However, other research on nudges to improve opioid prescribing found that introducing safety alerts in the EHR for when a patient was being co-prescribed an opioid and a benzodiazepine was not associated with changes in prescribing patterns (4). Overall, there are many open questions about the types of EHR-based alerts and reminders can effectively improve opioid prescribing patterns and pain treatment decisions.

Another important component of safe and appropriate opioid prescribing is the CDC guideline recommendation to check the PDMP to identify potentially problematic patterns of opioid use. A number of studies examine the effects of laws that mandate providers to check their state's PDMP on prescribing patterns and on opioid use patterns (5). Other research notes that many providers do not check the PDMP when prescribing opioids, or do so relatively infrequently (6-8). Reasons for the underuse of PDMPs by prescribers include that the data in the PDMP are difficult and time-consuming to access (7, 8). One approach to "nudge" providers to use the PDMP more frequently and effectively is to simply make it much easier to use, by integrating it directly into a patient's EHR. Very limited evidence to date exists on the effects of PDMP integration into the EHR (9). We are not aware of any randomized trials of PDMP integration into the EHR.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

Opioid-Naïve Population: Whether or not an opioid is prescribed in a primary care visit, *without* currently receiving a non-opioid alternative pain treatment (including a new order for a non-opioid pain treatment).

Current Opioid-User Population: A variable with three mutually-exclusive categories:

Category 1 (appropriate taper): Whether a primary care appointment with someone currently receiving a "high risk" opioid had an order that would reduce MME by no greater than 20%, relative to the current prescription, and there is documented evidence that the reduction was consistent with CDC guidelines. "High risk," is defined as a patient is currently receiving opioids with >50 MME and/or currently receiving both an opioid and a benzodiazepine.
Category 2 ("inappropriate" taper): Whether a primary care appointment with someone currently receiving a "high risk" opioid had an order that would reduce MME without documented evidence that the reduction was consistent with CDC guidelines, *or*, decreased MME by greater amounts than recommended (>20% relative reduction in MME).
Category 3 (no taper): Whether a primary care appointment with someone currently receiving a "high risk" opioid had no reduction in MME.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

Opioid-Naïve Population:

1) Whether a CDC-recommended non-opioid treatment is ordered in a primary care visit (e.g., referral to physical therapy, prescription of an NSAID, referral to pain clinic)
2) The length of opioid prescriptions
3) The MME of opioid prescriptions

Current opioid user Population:

1) Whether there was a partial reduction in the MME or prescription length of refill orders, versus a total opioid discontinuation
2) Whether there was an increase in the MME/day for current opioid users with at least 50 MME/day

All PCPs, including visits with opioid-naïve and current opioid-using patients:

1) The frequency with which PCPs check the PMP.
2) PCP satisfaction with decision support

Exploratory outcome:
For primary care appointments with someone currently receiving a "high risk" opioid, who did not get tapered, we will assess how frequently there is a documented clinical rationale for the decision to not taper, that is consistent with the CDC's guidelines. This outcome is not linked to the experimental study arms.

4.0 Study Intervention(s)/Interaction(s)

4.1 Description:

The subjects of the study are primary care clinicians working in Fairview and in University of Minnesota Physicians. The interventions to be tested in this study are

sets of EHR clinical decision support tools (some of which are referred to as, "Best Practice Alerts"). These tools are very similar to many other EHR tools and alerts that clinicians encounter and use in their practice, and which are frequently adopted by health systems.

There are two sets of interventions to be tested. Both of these intervention sets use behavioral economics principles around "choice architecture." One set includes a pair of EHR alerts – one that triggers for patients who are opioid-naïve (i.e., have not had an active opioid prescription in the past six months), and one that triggers for patients who are current opioid users. The other intervention is essentially the same for patients who are opioid-naïve or current opioid users.

These interventions will be delivered to all of the PCPs working in Fairview and UMP primary care clinics that are assigned to one of the intervention arms of the study (randomization arms are described in Section 5).

Detailed description of the Intervention Set A (choice architecture):

For the opioid-naïve group, the interventions will "fire" when a PCP initiates an opioid order within the EHR for a patient who has not had an opioid prescription within the past six months. The alert, shown in Exhibit 1a, provides guidance language about opioid prescribing and prompts the PCP to open the "SmartSet" to order non-opioid treatment alternatives. PCPs can choose to ignore this, but opening the SmartSet is the default option. When the SmartSet is opened, PCPs can choose to click on a variety of treatment order options, including both non-opioid pharmacological options and non-pharmacological options (e.g., referral to physical therapy or pain clinic). Clicking on a category expands the selections, and Exhibit 1b shows the SmartSet with the non-pharmacologic options expanded. The non-opioid treatment options were selected for the intervention based on the CDC's chronic pain recommendations and the Fairview Opioid Network Team's recommendations.

Exhibit 1a.

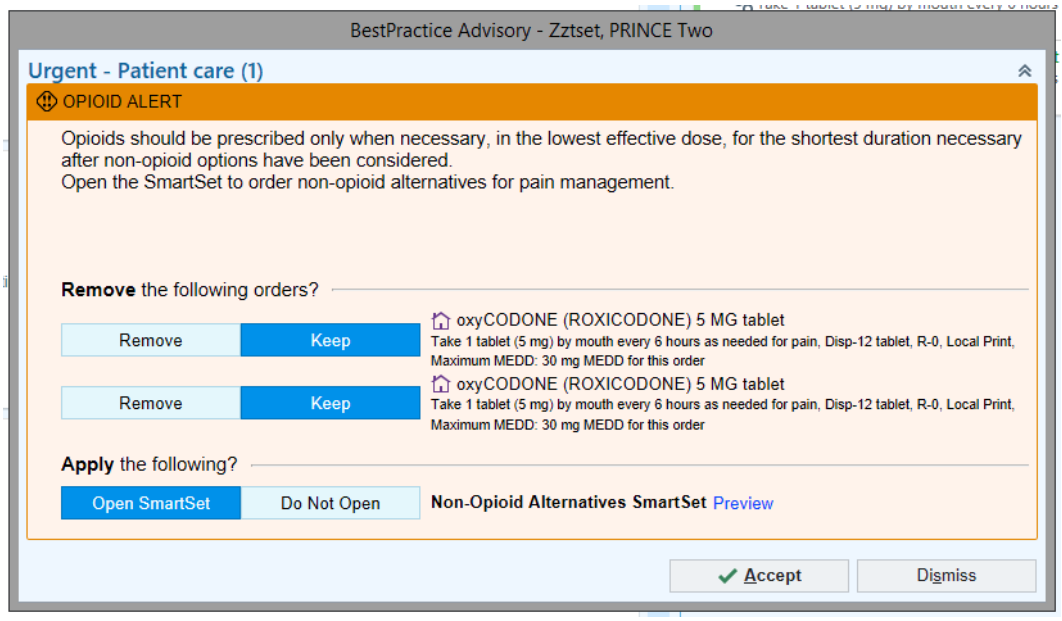
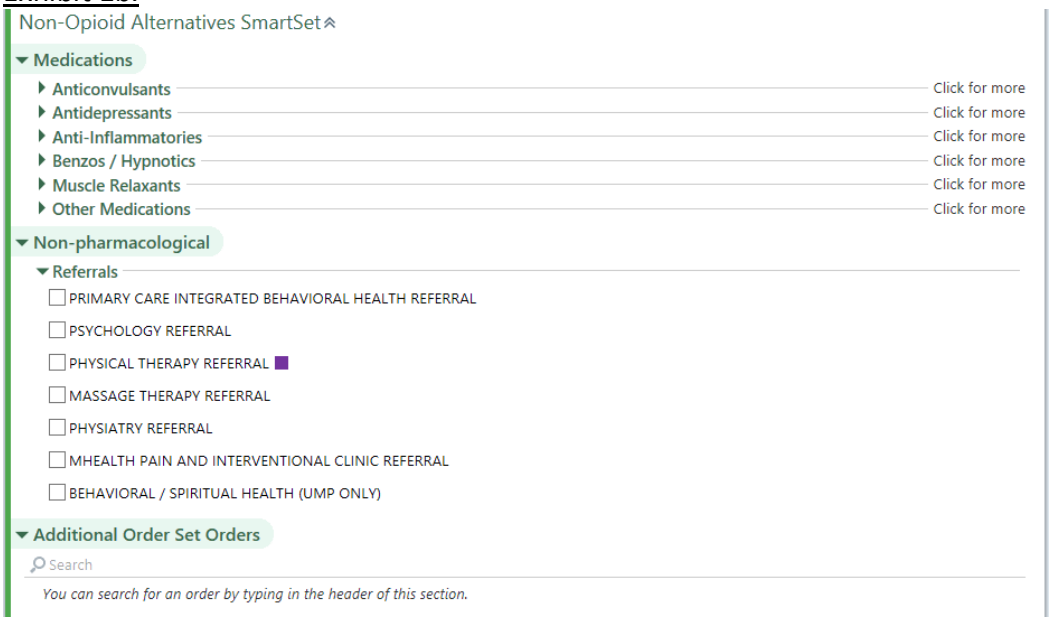
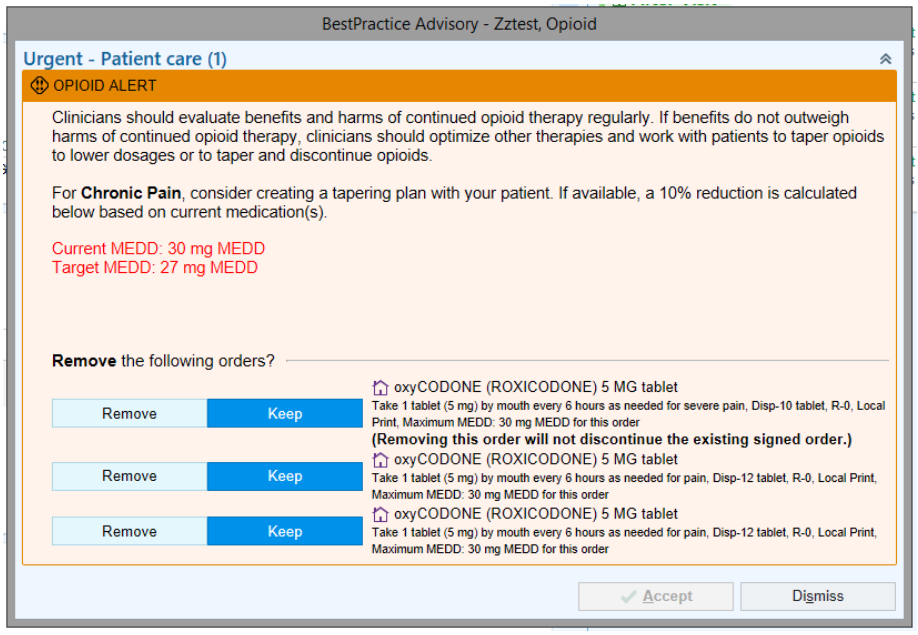


Exhibit 1b.



For the current-opioid user group, the interventions will "fire" when a refill order for an opioid is initiated or a new opioid order is initiated for a patient currently receiving an opioid. The alert, shown in Exhibit 2, prompts PCPs to consider tapering the patient's opioid. The alert also displays the MME of the patient's current opioid prescription and automatically calculates what a 10% reduction in MME relative to the current prescription would be. The alert contains options to either cancel the refill order, or to continue with the order.

Exhibit 2. View of the "opioid taper" alert.



Detailed description of the Intervention Set B (PMP Integration):

For all PCPs assigned to this intervention, they will have integrated access to the PMP embedded within the EHR. All clinicians can already access the PMP to look up a patient's prior opioid prescriptions and prescription fills. However, this process involves signing in to the separate PMP website and can be complicated and time-consuming within typical clinical workflow. The integrated PMP tool makes it much easier and faster for a PCP to access the PMP information for a given patient. This is a proprietary tool called "PMP Gateway," developed by Appriss, and is being paid for by the state of Minnesota. In this tool, there is a link that is embedded directly within the EHR, and does not require the PCP to re-enter credentials and password, and automatically shows the relevant information for the patient whose EHR is already open. We show screenshots for the integrated PMP tool below in Exhibits 4-5.

Exhibit 4. Accessing the integrated PMP in Epic

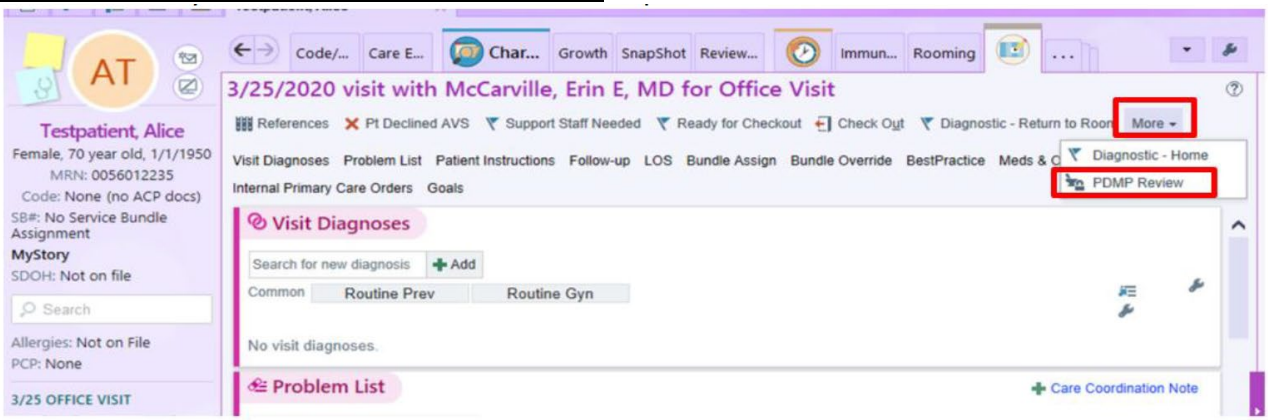
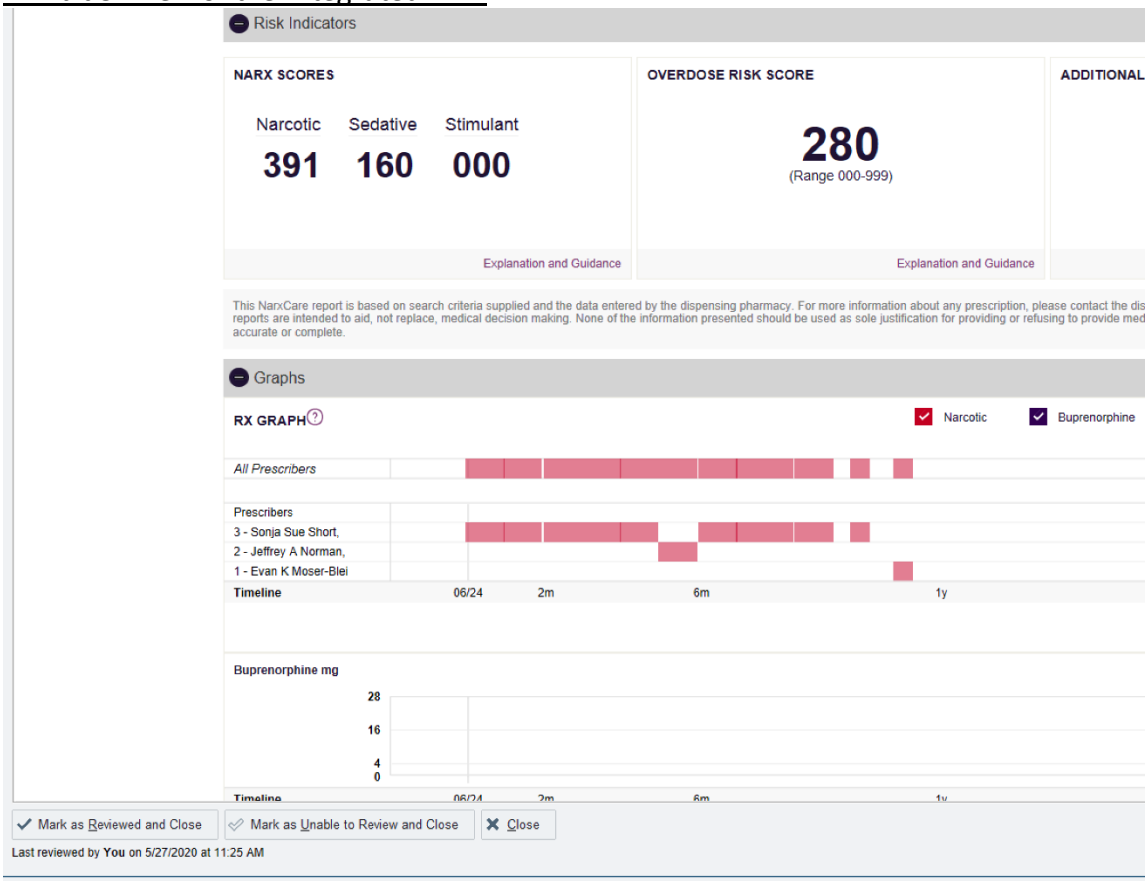
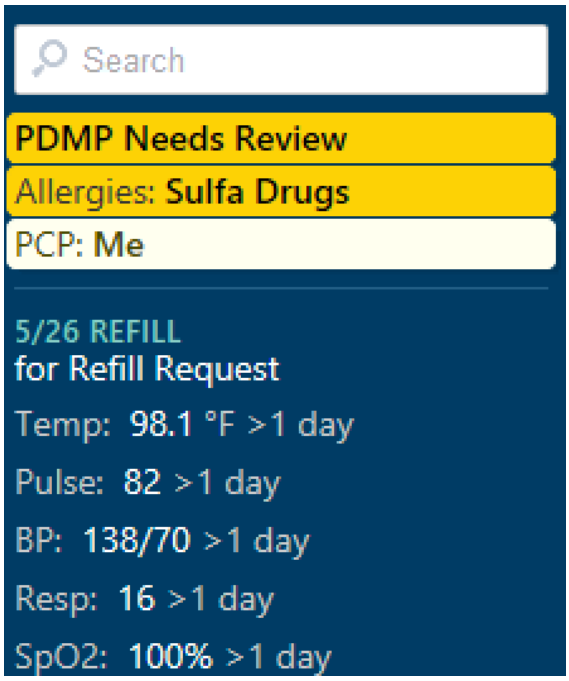


Exhibit 5. View of the integrated PMP



The integrated PMP tool also has a "reminder" function that we will use. This reminder is triggered if the PCP attempts to sign an opioid prescription in the EHR without having checked the PMP within the past 24 hours. A screenshot example of the PMP reminder is shown in Exhibit 6.

Exhibit 6. View of the PMP reminder



The study team will collect four types of data.

1) Passively-collected data from the Fairview and UMP EHR systems. These data involve no interactions with the participants, and is information that is already collected by Fairview IT as part of the EHR system.
2) Retrospective chart reviews of primary care visits with current opioid users. These chart reviews will involve no direct interaction with the study participants.
3) Passively-collected data from the Minnesota PMP. These data involve no interactions with the participants, and is information that is already collected automatically by the state of Minnesota.
4) Web survey data from participants. We will use the University of Minnesota's REDCap system to collect information from consenting primary care providers via web surveys. This will include basic demographic and background information, information about views on pain treatment and opioid prescribing, information about how providers interact with EHR systems, and information about satisfaction with clinical decision support for pain and opioid treatment. Web surveys will be fielded at the start and again at the end of the 12 month study period. All PCPs in the participating primary care clinics will be exposed to the study interventions their clinic is assigned to, regardless of whether PCPs complete the web survey or not.

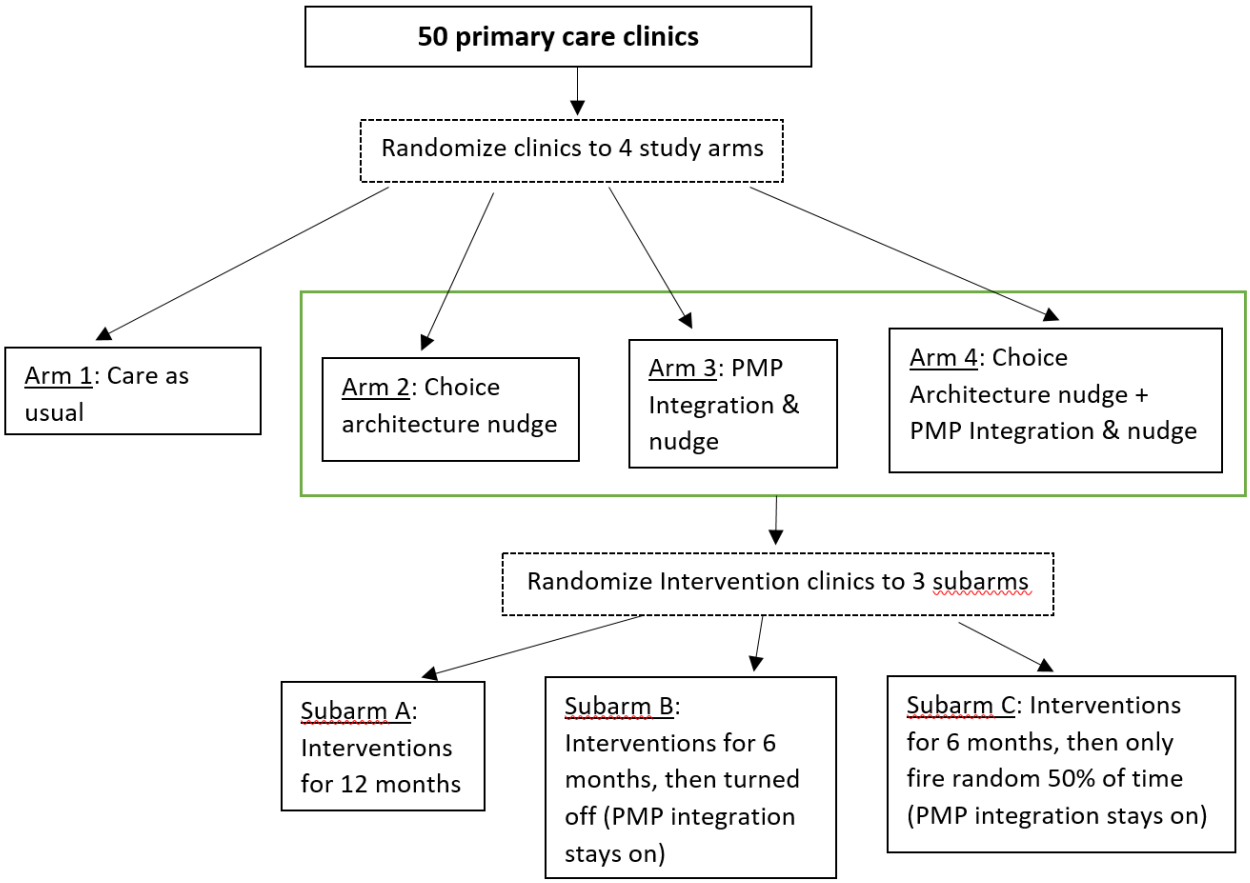
5.0 Procedures Involved

5.1 Study Design:

The study is a clinic-randomized trial of EHR clinical decision support tools for pain treatment and opioid prescribing. We propose clinic-level randomization in order to minimize the potential for spillovers or "contamination" of the intervention across the study arms.

The randomization plan is described in the figure below. There are two dimensions to the randomization. One dimension is treatment arm within a factorial study design: some clinics will be randomized to receive "care as usual," (Arm 1), some clinics will be randomized to receive Intervention set A (Arm 2), some clinics will be randomized to receive Intervention B (Arm 3), and some clinics will receive both Interventions A and B (Arm 4). The other dimension to randomization occurs among the clinics that are assigned to Intervention set A or B, and involves those clinics being randomized to three different conditions. 1) The clinic receives the intervention set for the entire 12 month study period (Subarm A), 2) the clinic receives the intervention set for only the first 6 months of the study period, and then reverts to "care as usual," for Intervention set A and PMP integration without the reminder function for Intervention B (Subarm B), or 3) The clinic receives the intervention set for the first 6 months, but in the second 6 months, Intervention set A will only fire in a random half of clinical encounters and the reminder function will only fire in a random half of clinical encounters for Intervention B (Subarm C).

Exhibit 7. Randomization plan



5.2 Study Procedures:

- All PCPs who are in clinics that are assigned to Intervention set A or B will receive communications from the Medical Directors of their respective clinics about the implementation of the new EHR alerts and/or PMP integration, in the same way that new best-practice alerts and EHR features are normally implemented in Fairview and UMP.
- All PCPs who are in clinics that are assigned to Intervention set A or B will receive either Intervention set A or B over the course of the study period. As described above, both Intervention Sets A and B are extremely similar to the types of best-practice alerts and/or new EHR capabilities that clinicians are currently exposed to in their usual clinical practice.
- The study team will receive bi-weekly reports from Fairview IT which will include data by study arm on how often the PRINCE alerts and PMP reminders are firing, and how often PCPs are using versus dismissing the alerts.
- All PCPs in the Fairview and UMP primary care clinics will be recruited to complete brief web surveys at the start and end of the 12-month study period. PCPs will be recruited to participate in these surveys via email communications from the study team, and written communications from the study team and from Fairview and UMP clinical leadership. These web surveys will not collect any personal health information. They will collect information on PCPs' background characteristics, knowledge and attitudes about pain treatment, opioid therapy, and practice guidelines, and satisfaction with clinical decision support for pain treatment and opioid prescribing. The web surveys will be implemented using the University of Minnesota's REDCap system.
- Data from the shared EHR of Fairview and UMP will be used for analysis. These data are already collected as part of clinical care, and the research team will access these data via the University of Minnesota's Informatics Consulting Service. The data that the Informatics Consulting Service already has on hand will be augmented with additional EHR data on the activation of the study's EHR alerts and the engagement with these alerts, along with data from the legacy HealthEast (which is now part of Fairview) Epic system which are not currently received by the Informatics Consulting Service. Fairview IT will share those data with the Informatics Consulting Service, who will merge it with the other EHR data that the Informatics Consulting Service already has. All of these data will be stored and accessed only on the ICS's secure data shelter.
- We will conduct retrospective chart reviews of the visit records for all visits where someone currently receiving a "high risk" opioid had an order that would reduce MME by no greater than 20% relative to the current prescription. The study team has already created the chart review tool that will be used. These chart reviews will ascertain whether there is any documentation of the clinical rationale for tapering that is consistent with the

CDC's guidelines. Each month during the 12-month study period, the study team will receive a new data extract from the AHC-IE, from which we will identify the relevant visits. We will record the Medical Record Number and visit date and store them in a database in the AHC-IE's server. At the conclusion of the 12 month study period, all of these files will be destroyed.

The PI will share that identifying information with the co-Investigator who will lead the chart reviews. For each visit that is reviewed, the study team will enter the information that is collected into a secure REDCap database. These data will then be shared with the ICS staff, who will link it to the EHR data in the ICS' secure data shelter.

- Data on the number of times per month each PCP checks the PMP, or has an assigned delegate check the PMP on their behalf, will be taken directly from the Minnesota PMP. The PMP data are held by the state of Minnesota Board of Pharmacy. The study team will email the PCPs in the study asking for electronic authorization to access their data on how frequently they and their delegates check the Minnesota PMP between August 2019 and September 2021.

  For the PCPs who provide this electronic authorization, Fairview IT will provide the Drug Enforcement Agency (DEA) prescriber identifier number to the PI. The list of DEA numbers will be transferred and stored via the PI's secure "BOX" account. The PI will then transfer the list of DEA numbers to the MN Board of Pharmacy, also using BOX for file transfer. The Board of Pharmacy will pull the data on monthly number of times the PMP was checked between August 2019 and September 2021, and then transfer back to the PI using BOX. The study team will analyze the PMP data on the PI's HIPAA-compliant secure server. The study team will link information on characteristics of the PCPs (i.e., provider type, clinic where they practice, treatment arm assignment, and baseline information from the web survey) with the PMP data, and then remove all identifiers from the analytic dataset. The file linking study identifiers to the PMP data will be stored separately in the PI's BOX.

- In addition, for primary care appointments with someone currently receiving a "high risk" opioid, who did <u>not</u> get tapered, we will assess how frequently there is a documented clinical rationale for the decision to not taper, that is consistent with the CDC's guidelines. We will do retrospective chart reviews of a random 10% sample of primary care appointments with someone currently receiving a "high risk" opioid, who did not get tapered (up to 2,000 visits). This will shed light on the appropriateness of decisions to not taper opioids among current users. For each visit that is reviewed, the study team will enter the information that is collected into a REDCap database.

5.3 Follow-Up:

At the end of the 12-month study period, participants will be invited to participate in a follow-up web survey that is similar in structure and length to the baseline survey.

The research team will also examine longer-term opioid prescribing patterns using the EHR data alone, up to 24 months after the completion of the study period.

5.4 Individually Identifiable Health Information:

This research will require exact dates of service for the EHR data from the AHC-IE. In addition, we will require Medical Record Numbers for the subset of the data collection that will involve chart reviews. Names and license numbers of the PCPs will be collected.

5.5 Modifications to Procedures in Response to Data Monitoring Committee recommendations:

The external Data Monitoring Committee reviewed the results of the interim outcomes analysis (see Section 17.1 for details). Their letter to the PI is now added to the study IRB files. We will follow their recommendations and implement two changes to the study procedures.

Change #1: Open up the PMP Integration arm to the entire study population at the 6-month mark.

Change #2: We will not implement the secondary randomization of the intervention arm clinics into three subgroups. Instead, the clinics assigned to the "choice architecture" intervention set in Arms 3 and 4 will stay the same for months 6-12 of the study period.

6.0 Data Banking

6.1 Storage and Access:

After the study is completed, the data will be transmitted to and stored by ICS, for use by other researchers including those outside of the study.

6.2 Data:

The following identifiable data elements will be stored after the study completion:

- Provider Names
- Dates, except year
- Geographic data
- Email addresses
- Medical record numbers
- Certificate/license numbers
- Any unique identifying number or code (ex: license numbers of the PCPs)

6.3 Release/Sharing:

Researchers submit a research proposal to the PI to assess scientific merit of proposed work and competing projects or initiatives. The PI or his designee communicates approval, disapproval, or request revisions.

Data will be released according to policies established and maintained by the University of Minnesota's Human Research Protection Program and ICS (here for more details) in compliance with all state, federal and institutional policies and guidelines. Data will be released after IRB determination and/or approvals are obtained.

7.0 Sharing of Results with Participants

7.1 Aggregate-level study results will be shared with clinical leadership from Fairview and UMP before any results are published in peer-reviewed journals. No identifying information will be shared.

8.0 Study Duration

8.1 We anticipate that:

- The duration of each participant's participation in the study will be 12 months.
- The process of enrolling participants to complete the web surveys will be three weeks for the baseline survey and three weeks for the follow-up survey.
- Once the 12-month study period has ended, the data analysis will take an additional 9-12 months.
- EHR data alone will be examined up to 24 months after the completion of the study period.

9.0 Study Population

9.1 Inclusion Criteria:

Primary Care Providers:

The final study sample for outcomes derived from EHR and PMP data will include all PCPs from all of the Fairview and UMP study clinics.

Retrospective chart reviews of primary care visits with current opioid users:

1. Male or female ≥18 years of age at the primary care visit
2. Current "high-risk" opioid user as defined by having a current opioid prescription with at least 50 MME/day and/or having a current opioid prescription along with a current benzodiazepine prescription.

9.2 Exclusion Criteria:

Primary Care Providers:

PCPs will be excluded from the final analytic sample if they work less than 20% FTE.

Retrospective chart reviews of primary care visits with current opioid users:

Patient records corresponding to each PCP will only be included in the analysis if the patient has Minnesota Research Authorization.

9.3 Screening:

Information on which PCPs work in the study clinics will be provided by staff from Fairview and UMP. Information on which patient records have Minnesota Research Authorization will be provided by the AHC IE staff.

10.0 Vulnerable Populations

10.1 Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be targeted, included (not necessarily targeted) or excluded from participation in the study.
Children	Excluded from Participation
Pregnant women/fetuses/neonates	Included/Allowed to Participate
Prisoners	Excluded from Participation
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Excluded from Participation
Non-English speakers	Excluded from Participation
Those unable to read (illiterate)	Excluded from Participation
Employees of the researcher	Excluded from Participation
Students of the researcher	Excluded from Participation

Undervalued or disenfranchised social group	Excluded from Participation
Active members of the military (service members), DoD personnel (including civilian employees)	Excluded from Participation
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Excluded from Participation
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	Excluded from Participation
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Excluded from Participation
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	Excluded from Participation
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	Excluded from Participation

10.2 Additional Safeguards:

This study focuses on PCPs. Though we are requesting a waiver of informed consent for participation in the overall study which involves exposure to the study intervention arms, and analysis of passively-collected data (per Section 22.2). We will be obtaining modified web-based consent for the portion of the study where we will collect information from PCPs via web surveys. The information form for

the web surveys will make clear that supervisors will not know whether or not PCPs have participated in the study and that there are no negative consequences for not participating in the web surveys.

This study will likely include some PCPs who happen to be pregnant during the study. We think that the risk for this population is minimal, as the interventions are just EHR tools to improve opioid prescribing practices, and should have no bearing on the health of the PCP participants in any way.

11.0 Number of Participants

11.1 Number of Participants to be Consented:

We expect to enroll approximately 300-350 PCPs in both the baseline and follow-up web surveys.

We expect that 400-450 PCPs will be included in the final analytic samples for the analysis of EHR data and PDMP data.

We expect that 20,000 charts will be reviewed in the retrospective chart reviews of primary care visits with current opioid users.

12.0 Recruitment Methods

12.1 Recruitment Process:

All PCPs in Fairview and UMP primary care clinics will be included in the study. Those who are in the three intervention arms will receive information about the interventions that are going to be delivered in their clinics.

Active recruitment of participants will only be relevant for the web survey components of the study. We will recruit all active PCPs who are working in the Fairview and UMP primary care clinics.

We will include two notices about the upcoming web surveys in Fairview's weekly "Neighborhood News" newsletter. The Medical Director of each primary care clinic will email their respective PCPs 1-4 days prior to the first survey invitation, explaining that all of the PCPs in the clinic will be receiving emails from the study team about participating in the web survey.

The research team will email all of the eligible PCPs directly to recruit them into the web survey. We will use the RedCap system to manage email invitations so that reminders will only be sent to people who have not yet responded to the survey. The first invitation will be sent two weeks prior to the start of the PRINCE interventions being activated. The second invitation will be sent one week prior to the start of the PRINCE interventions being activated. The third and final email invitation will be sent the day after the PRINCE interventions are activated.

The research team will email all of the eligible PCPs directly to recruit them to provide authorization for access to data on their PMP usage. We will use the RedCap system to manage email invitations so that reminders will only be sent to people

who have not yet responded to the survey. We will send an introductory email, followed by up to three follow-up emails in the three weeks after the introductory email.

12.2 Source of Participants:

We will obtain the list of all PCPs working in the Fairview and UMP primary care clinics from both Fairview and UMP clinical leadership.

12.3 Identification of Potential Participants:

- The PI has obtained the current list of all PCPs in Fairview and UMP primary care clinics, along with email addresses. This information was shared by Fairview and UMP clinical leadership.
- Each primary care clinic's Medical Director will first alert all of their respective PCPs about the PRINCE study and the web surveys. The study team will then contact the PCPs directly via email to recruit the PCPs for the web surveys.
- For the analysis of EHR data, along with the subset of visits that are identified for medical chart reviews, we will be restricted by the AHC-IE to only obtain data from patient records where there is Minnesota Research Authorization status.

12.4 Recruitment Materials: The following recruitment materials will be used in this study:

- communications from the Medical Directors
- email communications from the study team to recruit PCPs for the brief web surveys
- written communications from the study team to Fairview and UMP clinical leadership
- notices about the upcoming web surveys to be published in Fairview's "Neighborhood News" newsletter.
- Email communication from the Medical Directors to PCPs about the authorization for accessing PMP data.
- Email communications from the study team to the PCPs to ask for authorization for accessing PMP data.

Recruitment materials are attached.

12.5 Payment:

- Each PCP that completes the web survey will be compensated $250. PCPs will be eligible to receive this payment for both the baseline and 12-month follow-up surveys, up to a maximum of $500.
- The research team will mail checks directly to the participating PCPs 2-4 weeks after the completion of the survey.

13.0 Withdrawal of Participants

13.1 Withdrawal Circumstances: There are no anticipated circumstances under which participants will be withdrawn from the research without their consent. PCPs will not have the ability to withdraw from the study intervention arm their clinic is assigned to. However, the nature of the interventions is that they are EHR-based nudges that can easily be ignored by the PCP, with no negative consequences to either the PCP or to the study.

13.2 Withdrawal Procedures: Participants will be free to withdraw from completing the web surveys at any time, although their EHR data would still be used for analysis.

13.3 Termination Procedures: N/A

14.0 Risks to Participants

14.1 Foreseeable Risks:

The only potential foreseeable risks are

a) a data security breach, which we consider a minimal risk due to our data security plan. The records of this study will be kept private. In any sort of report we might publish, we will not include any information that will make it possible to identify a subject. Research records will be stored securely and only researchers will have access to the records.

b) discomfort answering web survey questions, which we consider a minimal risk because the web survey is designed to avoid questions that might make respondents uncomfortable and because respondents can choose to not respond to any survey question, and

c) that the interventions themselves may be a minor nuisance in their day-to-day clinical practice. We think that latter risk is minimal because the EHR interventions can be ignored with no negative implications for the PCPs or for the study data and because these interventions are very similar to EHR alerts that are routinely used and introduced in clinical practice.

14.2 Reproduction Risks:

Not Applicable.

14.3 Risks to Others: Not Applicable

15.0 Incomplete Disclosure or Deception

15.1 Incomplete Disclosure or Deception:

- This research will not involve incomplete disclosure or deception.

16.0 Potential Benefits to Participants

16.1 Potential Benefits: We do not foresee any immediate direct benefits to participants.

Potential benefits include helping to improve the design of and future investment in EHR-based tools to improve pain treatment in primary care which may improve the

experience using the EHR for PCPs and may improve outcomes for patients with pain symptoms, as well.

17.0 Statistical Considerations

17.1 Data Analysis Plan:

The first formal statistical interim analysis is planned on the primary endpoint. This interim analysis is planned to take place when the study is at least 4 months into the study period.

Formal interim analyses of the data will be reviewed by the Data Monitoring Committee. The Committee will be asked to give advice on whether the accumulated data from the study, together with results from other relevant studies, justifies continuing exposure to the study interventions. A decision to modify or discontinue all or some portions of the study will be made only if the result is likely to convince a broad range of experts. In mid-January, 2020, the Data Monitoring Committee will meet to review the interim outcomes analysis.

The final analysis for the primary outcome is planned to take place 12-months after study. The first main report/publication of the study will be prepared when PCPs have completed the 12-month follow-up survey and data for the primary endpoint has been received and cleaned. Longer-term endpoints will be analyzed when all data has been received and cleaned.

An independent Data Monitoring Committee (DMC) will ensure the integrity throughout the study by reviewing outcome data for the study interventions. The DMC will be comprised of a statistician, an expert in behavioral economics interventions in a clinical setting, and a physician with expertise in trials around opioid prescribing interventions. The DMC will review interim and final analysis, data quality and completeness, external factors such as scientific advances which may impact the study and make recommendations. Stopping rules for efficacy or futility will be specified in the charter at the beginning of the study.

Interim Outcome Analysis Plan

The DMC is responsible for assessment of the efficacy of the interventions during the course of the study i.e. interim analyses of efficacy endpoints. The study protocol version 1.2 pre-specifies the following interim analyses: The DMC will be asked to recommend graduation to the second stage of randomization when there is clear and substantial evidence of a treatment difference. As a guideline, the Lan-DeMets spending function analog of the Pocock boundaries will be used to monitor the primary endpoint comparison for the primary aims. The statistical analysis plan is given in the protocol. In brief, we will fit mixed effects logistic regression models of the primary outcome (described below) for opioid-naïve patients using data from the 12 months of the pre-intervention period, and through December 31, 2020 (approximately 4 months of post-intervention data). These models will include fixed effects for whether or not the encounter was at a clinic in the intervention a given intervention arm or received both interventions, indicators for study month to account for secular trends, and an indicator for whether an observation takes place in an intervention arm clinic and in the post-intervention period. These models will include random effects for clinic and PCP (nested in clinic) to account for within-clinic and within-PCP correlation.

We propose a single interim analysis occurring sometime shortly after January 1, 2021, using data through December 31, 2020. The planned boundaries are given below. The advantage of using the Lan-DeMets spending function is that this permits the DMC during the course of the study to require more frequent interim analysis and preserve type I error. If more interim analyses are desired by the DMC, the Lan-DeMets spending function will be recalculated and provided with each DMC report.

Interim Analysis	Critical Z-score	Nominal One-sided p-vale	Alpha Spent
1	2.16	0.0155	0.0155
Final	2.20	0.0139	0.0095

The analysis of the effect of the intervention on key secondary outcomes will also be provided. Should the stopping boundary be crossed at the proposed interim analysis and there is clear evidence of an intervention's effect, we would recommend the DMC to move into phase 2 of the study in which clinics in the experimental arms for that intervention would be re-randomized to continue with intervention for all opioid prescription or for only 50% of opioid prescriptions. The decision to move to phase 2 will be made separate for each intervention component (choice architecture nudge and PDMP integration/reminders).

We emphasize that data will only be available for the primary outcome in a timely manner for the opioid naïve subpopulation and, therefore, decisions on whether or not to move into stage two of randomization will be made based on that subpopulation only.

The primary outcome for the opioid-naïve subpopulation is: Whether or not an opioid is prescribed in a primary care encounter, *without* currently receiving a non-opioid alternative pain treatment (including a new order for a non-opioid pain treatment).

Key secondary outcomes to be presented to the DMC are:

- The frequency with which each PCP checks the Minnesota Prescription Drug Monitoring Program (derived from the Minnesota PDMP).
- For the opioid-naïve subpopulation, whether a CDC-recommended non-opioid treatment is ordered in a primary care visit (e.g., referral to physical therapy, prescription of an NSAID, referral to pain clinic)
- For the opioid-naïve subpopulation, the length of opioid prescriptions
- For the opioid-naïve subpopulation, the MME of opioid prescriptions

Additionally, there is a possibility that data on two secondary outcomes for the current opioid-using subpopulation will be presented to the DMC:

- Whether there was a partial reduction in the MME or prescription length of refill orders, versus a total opioid discontinuation

- Whether there was an increase in the MME/day for current opioid users with at least 50 MME/day

If at the single interim efficacy analysis, the PDMP integration/reminder intervention show substantial efficacy, we would recommend that the PDMP integration be made available to all clinics. A decision on what constitutes substantial efficacy will be made in consultation with the DMC.

Futility Analysis

There will be no formal futility analyses presented to the DMC. Given that these intervention have small potential adverse effects, the DMC will NOT be asked to recommend early termination for futility.

17.2 Power Analysis: The proposed design has sufficient power to detect clinically meaningful changes in opioid prescription practices from the main effects of the two interventions and the control group (10). All power calculations assume a two-sided test at the 0.05 significance level. Power for the Primary Aim (comparison of intervention arms to the control during months 1-6) is shown in Exhibits 2a-b assuming a total of 48 clinical are randomized (equal allocation between Arms 1-4) with a conservative estimate of 10 providers per clinic (~12 providers per clinic in the FHS/UMP system). The range of the number of visits eligible and the percentage of visits with an opioid prescription in the control arm (for both the opioid-naïve and opioid-using populations) were based on preliminary data from the EHR from a subset of clinics that will be randomized. Meeker et al. (1) assumed an intra-clinic correlation of 0.05 but that encounters within the same provider were not further correlated. We assumed the correlation for visits within the same clinic (but with different providers) was 0.025 and the within-provider correlation would be 0.075 as well as considering a more conservative scenario (correlation given on the logistic scale (11)). We assumed a 5% and 17% prescription rate in the control arm for the opioid-naïve and opioid-using populations, respectively, based on preliminary analysis of opioid prescribing in Fairview primary care clinics, and based on published research (12). We considered a difference in the percentage of eligible encounters with an opioid prescription between the intervention and control groups of 3.5% and 5% to be of clinical interest in the two populations. Exhibits 8 and 9 demonstrate that we have sufficient power across a wide range plausible scenarios and maintain adequate power even under smaller effect sizes. These calculations are also conservative as they assume 48 clinics, whereas we expect to enroll over 50 clinics.

We also have sufficient power to detect differences between 2.5 to 4 percentage points across the two intervention sets during the first 6 months of the intervention.

Exhibit 8. Power to detect a difference in proportion of eligible visits with an opioid prescription between intervention and control arms. Power calculations assume an opioid prescription rate in the no intervention arms of 7%.

30 eligible visits/month/provider					15 eligible visits/month/provider				
	% reduction in opioid prescribing					% reduction in opioid prescribing			
Intra-clinic/ Intra-provider correlation	15%	20%	25%	30%	Intra-clinic/ Intra-provider correlation	15%	20%	25%	30%
0.025/0.075	96%	100%	100%	100%	0.025/0.075	76%	95%	100%	100%

Exhibit 9. Power to test a difference in proportion of eligible visits resulting in an opioid prescription between intervention and controls arms in opioid-using population (Primary Aim). Power calculations assume 40 clinics randomized equally to Arms 1-4 with 10 providers/clinic, the opioid prescription rate in the control arm was 17%.

10 eligible visits/month/provider				5 eligible visits/month/provider			
	Difference in opioid prescription rate between control and intervention				Difference in opioid prescription rate between control and intervention		
Intra-clinic/ Intra-provider correlation	4.5%	5%	5.5%	Intra-clinic/ Intra-provider correlation	4.5%	5%	5.5%
0.025/0.075	81%	89%	95%	0.025/0.075	77%	86%	93%

17.3 Statistical Analysis:

We will first empirically verify that randomization was successful by testing whether trends in the outcome are equal across the study arms in the 12 months prior to the start of the intervention period. Second, we will present descriptive statistics by intervention arm of the outcomes, basic characteristics of the PCPs, and clinical and demographic characteristics of the patients seeking care whose visits meet the inclusion criteria. We will also produce graphs of the unadjusted trends in the outcomes by month over the study period, and broken down by study arm.

We will run separate analyses for the opioid-naïve population and the current opioid user population. The analysis sample for the opioid-naïve population will be primary care visits for patients who have not had an active opioid prescription in the six months prior to the visit, and no cancer diagnosis in the 12 months prior to the visit. In order to identify the visits that plausibly might lead to an opioid prescription, we will restrict to primary care visits that have a recorded diagnosis that occurs regularly in opioid-prescribing visits. We are defining those diagnoses as diagnoses that were associated with at least a 3% opioid prescribing rate among opioid-naive primary care visits across all FMG and UMP primary care clinics over a 12 month period and there were at least 25 opioid orders in visits with the diagnosis for all visits in the study clinics during the 12-month period before the study, excluding diagnoses for current opioid use, which is intended to have very high sensitivity for capturing chronic pain-related diagnoses, but low specificity. We have already created this list, which includes 294 specific diagnoses with pain-related diagnoses the most common.

The analysis sample for the current opioid user sample will be all primary care visits for patients with an active opioid prescription, excluding patients with a cancer diagnosis in the 12 months prior to the visit. We will include both in-person visits along with virtual (telephone or video) visits for all analyses.

Primary Outcome Analysis

To test our primary hypotheses, we will fit mixed effects logistic regression models using data from the 12-month pre-intervention period, and the post-intervention period prior to any second-stage randomization (the model for the current "high risk" opioid group will be multinomial logistic regression due to the 3-category outcome). All models will include fixed effects for whether the encounter was at an intervention arm clinic, an indicator for whether the measurement was after the interventions began, and their interaction. The interaction is the primary measure of the intervention effect. These models include random effects for clinic and PCP (nested in clinic) to account for within-clinic and within-provider correlation. Because of the cluster-randomized design with a moderate number of clinics, residual imbalances in patient and PCP-characteristics among the randomized groups may exist. The primary analysis model will adjust for characteristics at all levels of the hierarchy including clinic-level (indicators for the four systems), PCP-level (clinician type [MD/DO, NP, or PA], sex, and length of tenure in medicine), and patient-level (age, sex, race/ethnicity, insurance status, and in-person or virtual visit). Separate models will be fit to assess the PDMP integration and choice architecture intervention and for the opioid-naïve and current, high-risk opioid users. In each model, the intervention group pools across two arms of the factorial design (e.g., the choice architecture intervention pools across arms 2 and 4) and the control condition pools across the remaining two groups (e.g., arms 1 and 3 to continue the example). A Bonferroni correction will adjust inference for multiple comparison across two different populations (opioid naïve and current, high-risk opioid users) but we will not adjust for multiple tests across the two different interventions.

As an exploratory analysis, we will assess whether PCP characteristics (clinician type and tenure in medicine) and patient characteristics (age, sex, and race/ethnicity) moderate the interventions' effect. Tests for treatment effect heterogeneity will be implemented by adding the interaction between the potential moderator and the intervention indicator to the models for the primary

outcome (adjusting for the same factors described above). The effect of the intervention within subgroups formed from the potential moderators will be estimated by fitting separate models within each subgroup.

Subgroup analyses will not be adjusted for multiple comparisons; they are supportive to the primary outcome analysis. Subgroup analyses will be interpreted with caution due to limited power and uncontrolled type I error.

If the study proceeds to the second stage of randomization, we will fit mixed effects logistic regression models using data from 12 months pre- and post-intervention. All models will include fixed effects for intervention arm (control, continued intervention, 50% intervention, or intervention turned-off), indicators for whether the measurement was after the initial interventions began or after the second stage randomization, and their interaction. The interaction is the primary measure of the intervention effect. The models will include the same random effects and covariate adjustment as above.

Secondary Outcomes Analysis: PDMP and Web Survey data
For other EHR-derived secondary outcomes, we will use the same general modeling framework as for the primary outcome but will fit mixed effects logistic or linear models depending on whether the outcome was categorical or continuous.

To assess intervention effects on the frequency of checking the PDMP we will fit mixed effects Poisson regression models using data from the 12 months pre- and post-intervention. All models will include fixed effects for whether the PCP was at an intervention arm clinic, indicator for whether the month was during the intervention period, and their interaction. The models will adjust for clinician type, length of tenure in medicine, and health system indicators, and include random effects for clinic and PCP (nested in clinic) to account for within-clinic and within-provider correlation. As an exploratory analysis, we will assess whether PCP characteristics (clinician type and length of tenure) moderate the effect of the interventions using a similar process as the primary outcome.

A similar approach will be used for the web survey data, except we will fit mixed effect linear regression models using data from the pre- and post-intervention surveys. All models will include fixed effects for whether the PCP was at an intervention arm clinic, an indicator for whether the survey was the 12-month follow-up, and their interaction.

17.4 Data Integrity: See section 20.2 Data Safety Monitoring

18.0 Health Information and Privacy Compliance

18.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

☐ I am requesting that all research participants sign a HIPCO approved HIPAA

Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☒ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research:

The analysis of patient records will be restricted to patients with Minnesota Research Authorization. The University of Minnesota AHC IE staff will only share records with us where there is Minnesota Research Authorization.

☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

18.2 Identify the source of Private Health Information you will be using for your research (Check all that apply)

☒ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

☒ I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☒ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☒ Other. Describe: Data on the number of times per month each PCP checks the PMP, or has an assigned delegate check the PMP on their behalf, will be taken directly from the Minnesota PMP. The PMP data are held by the Minnesota Board of Pharmacy. The study team will securely share the names and DEA numbers of the PCPs in the PRINCE study with the Board of Pharmacy, and the Board of Pharmacy will securely share the data back with the PI for analysis.

18.3 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.

The Informatics Consulting Service will only provide the research team with records of patients who have Minnesota Research Authorization status.

Fairview IT will only provide the research team with DEA numbers for PCPs that have authorized access to their PMP data, and the Minnesota Board of Pharmacy will only share PMP usage data for PCPs who have provided electronic authorization for access to their data.

18.4 Approximate number of records required for review:

For the chart review component of the study, we anticipate reviewing up to a total of 20,000 records using our chart audit tool. These records will need to be retrieved directly from Epic because the information we will extract is most likely in the providers' notes and assessments.

18.5 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

☒ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

We will recruit PCPs into the web survey component of the study by email that will be sent from the study team via RedCap. We will recruit PCPs to provide authorization for access to their PMP data by email that will be sent from the study team via RedCap.

18.6 Access to participants

The research team will only be accessing EHR data and medical records from patients who have Minnesota Research Authorization status.

18.7 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☒ In the data shelter of the Information Exchange (IE)

☒ Store ☒ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☒ In REDCap (recap.ahc.umn.edu)

☒ Store ☒ Analyze ☐ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In OnCore (oncore.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In the University's Box Secure Storage (box.umn.edu)

☒ Store ☐ Analyze ☒ Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

☐ Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:

☐ Store ☐ Analyze ☐ Share

☒ Other.

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions

The PDMP data analysis will take place on a Microsoft virtual server that resides in the Office of Information Technology (OIT) Data Center. The server location is "HPM-RHRC2.ad.umn.edu". Server operating system is maintained by OIT staff. Access to the data center is controlled and monitored.

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☐I will use a mobile device such as an tablet or smartphone not previously listed

18.8 Consultants. Vendors. Third Parties.

We will share some information on PCPs with the Minnesota Board of Pharmacy, for them to extract PDMP usage data. The information will include the names and DEA numbers of the PCPs.

18.9 Links to identifiable data: The PI has the full list of Fairview and UMP PCPs, including names. Once the web survey data is collected, baseline web survey information will be transferred to the AHC-IE and the study team will link some baseline survey data to the EHR data for analyses, using PCP name as a linkage. After the data are linked, PCP names will be removed from the data.

Medical record numbers are needed to identify the records for the chart audits, and to then link that information back to AHC-IE data. The list of Medical record numbers will be stored on the AHC-IE's secure server. The PI will only share those Medical record numbers with the co-Investigator David Satin who will lead the chart audits. Once the chart audits are completed, the chart audit data will be linked back to the rest of the AHC-IE data and the Medical record numbers will be deleted from our files.

18.10 Sharing of Data with Research Team Members. EHR data will only be accessed via the AHC-IE server. Only team members who are directly involved with data analysis will have access to these data.

18.11 Storage and Disposal of Paper Documents: There will be no paper documents with research data as part of this study.

19.0 Confidentiality

19.1 Data Security: All study team members who will access any of the study data will have completed the appropriate HIPAA training and CITI Human Subjects Protections trainings. All study data will be stored on password-protected servers with two-factor authorization.

20.0 Provisions to Monitor the Data to Ensure the Safety of Participants

20.1 Data Integrity Monitoring.

- The study team will conduct monthly reviews of data reports from Fairview IT, in order to assess whether the PRINCE alerts are firing as intended, and to assess the degree of PCP engagement with the alerts (e.g., how often using versus dismissing alerts).
- The study team will receive monthly EHR data extracts from the AHC-IE, and the study partners at MMB will receive weekly PDMP data extracts. This will allow us to do an interim outcome check using data collected through December 31, 2020.

20.2 Data Safety Monitoring.

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events.

21.0 Compensation for Research-Related Injury

21.1 Compensation for Research-Related Injury: N/A

Contract Language: N/A

22.0 Consent Process

22.1 Consent Process (when consent will be obtained): N/A

22.2 Waiver or Alteration of Consent Process (when consent will not be obtained, required information will not be disclosed, or the research involves deception):

- For participation in the overall study by PCPs (exposed to the study interventions), we are requesting a waiver of consent. Per the Common Rule (§46.116), informed consent can be waived when, "1) The research involves no more than minimal risk to the subjects; (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects; [and] (3) The research could not practicably be carried out without the waiver or alteration." We believe that we meet all three conditions, as we elaborate below.
- Common Rule Criterion 1 (Research involves no more than minimal risk). The proposed research is implementing a clinical quality improvement intervention. Clinical QI interventions that remind clinicians of practice guidelines and encourage clinical decisions that are concordant with well-established practice guidelines are common, and already carry minimal risk. In order to increase the value of the knowledge from the QI intervention, we will be randomly assigning clinics to receive different types of QI interventions. In addition, the specific nature of the proposed interventions further ensures that there is no more than minimal risk. By definition, the QI interventions to be tested do not compel any activity or decision by clinicians. Rather, they are designed to merely "nudge," clinicians towards evidence-based care that is supported by consensus guidelines from the CDC.
- Common Rule Criterion 2 (Waiving consent will not adversely affect the rights and welfare of the subjects). This study is merely applying randomization to a QI intervention that would already be deemed acceptable for clinical operations, without requiring consent from clinicians. Because this is a QI intervention that would normally be implemented without clinician consent, implementing the intervention to a random subset of clinicians will not adversely affect the rights and welfare of the subjects.
- Common Rule Criterion 3 (The research could not practicably be carried out without the waiver or alteration). As this study is a rigorous evaluation of a QI intervention, it is imperative to have information from all clinicians working in

the study clinics. Seeking out consent from all of the clinicians would be disruptive to the operations of the clinics. And, clinicians who would be willing to take the extra time to consent for the study would be different from those who do not. As such, the study sample would be biased towards only including the most motivated clinicians, which would undermine the value of the study, making the research not practicable.

22.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained):

- For the web survey component of the study only, we will obtain informed consent from PCPs but waive the signed documentation of consent. Because this study component is web-only, the consent process will be online-only. The first webpage of the web surveys will be the "information sheet" about the study, and at the end of the form participants will type their name to electronically "consent" to participation and move on to the actual web survey.
- Participants will have the opportunity to carefully review the information sheet and ask questions prior to participating. The PCPs will have the opportunity to discuss the study with others or think about it prior to agreeing to participate if needed. The PCPs may withdraw consent at any time throughout the course of the study and/or survey.
- We request a waiver of written/signed documentation of consent because we will be using an online consent process, where the typed signature of the participant on the front page of the web survey will be used for consent.

22.4 Non-English Speaking Participants:

- N/A

22.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

- Not applicable.

22.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

- Not applicable.

22.7 Adults Unable to Consent:

- Not applicable.

23.0 Setting

23.1 Research Sites:

- All of the potential participants in the study will be PCPs working in Fairview or UMP primary care clinics.

- The web surveys will be conducted on the work or personal computers of the PCPs. The trial interventions will take place within the EHR of each PCP in Fairview and UMP primary care clinics.
- Data analysis of the EHR data and the web survey data will be conducted at the University of Minnesota Division of Health Policy and Management, and on the AHC-IE's servers.
- Data analysis of PMP data will be conducted at the University of Minnesota Division of Health Policy and Management.

23.2 International Research:

Not applicable.

23.3 Community Based Participatory Research:

- Not applicable.

24.0 Multi-Site Research

Not applicable.

25.0 Coordinating Center Research

Not applicable.

26.0 Resources Available

26.1 Resources Available:

- This project is funded by an R33 grant from NIDA, over a three year period. The PI's project time is funded at 30% FTE for all three years. All co-Investigators are funded at levels from 5%-15% FTE over the three year period. There is also a 50% FTE Project Manager and a 50% FTE doctoral student research assistant.
- For the primary outcomes, we will have EHR data on all of the PCPs who are working in the study clinics. We expect this will include approximately 400 PCPs. For the web survey component, we expect a 75% response rate.
- The research team has all of the required statistical software and computing resources needed to complete the research, including departmental resources and the AHC-IE's resources.
- All people assisting with the research will be required to undergo training in the research background, objectives, and procedures. The PI will be responsible for clearly delineating all duties and functions of the entire research team.

27.0 References

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