De-Implementing Opioid Use and Implementing Optimal Pain Management Following Dental Extractions

Protocol Number: 17-085-E

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.1 Synopsis; 1.3 Schedule of Activities	Extended the enrollment period.	Due to the impact of COVID-19 on care delivery, the enrollment period will be extended to meet patient accrual goals.

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SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigators:

Signed:  Date: 12-28-2020

Name: **D. Brad Rindal, DDS**

Title: Co-Principal Investigator

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), and the National Institute of Dental and Craniofacial Research Terms and Conditions of Award

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the HealthPartners Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

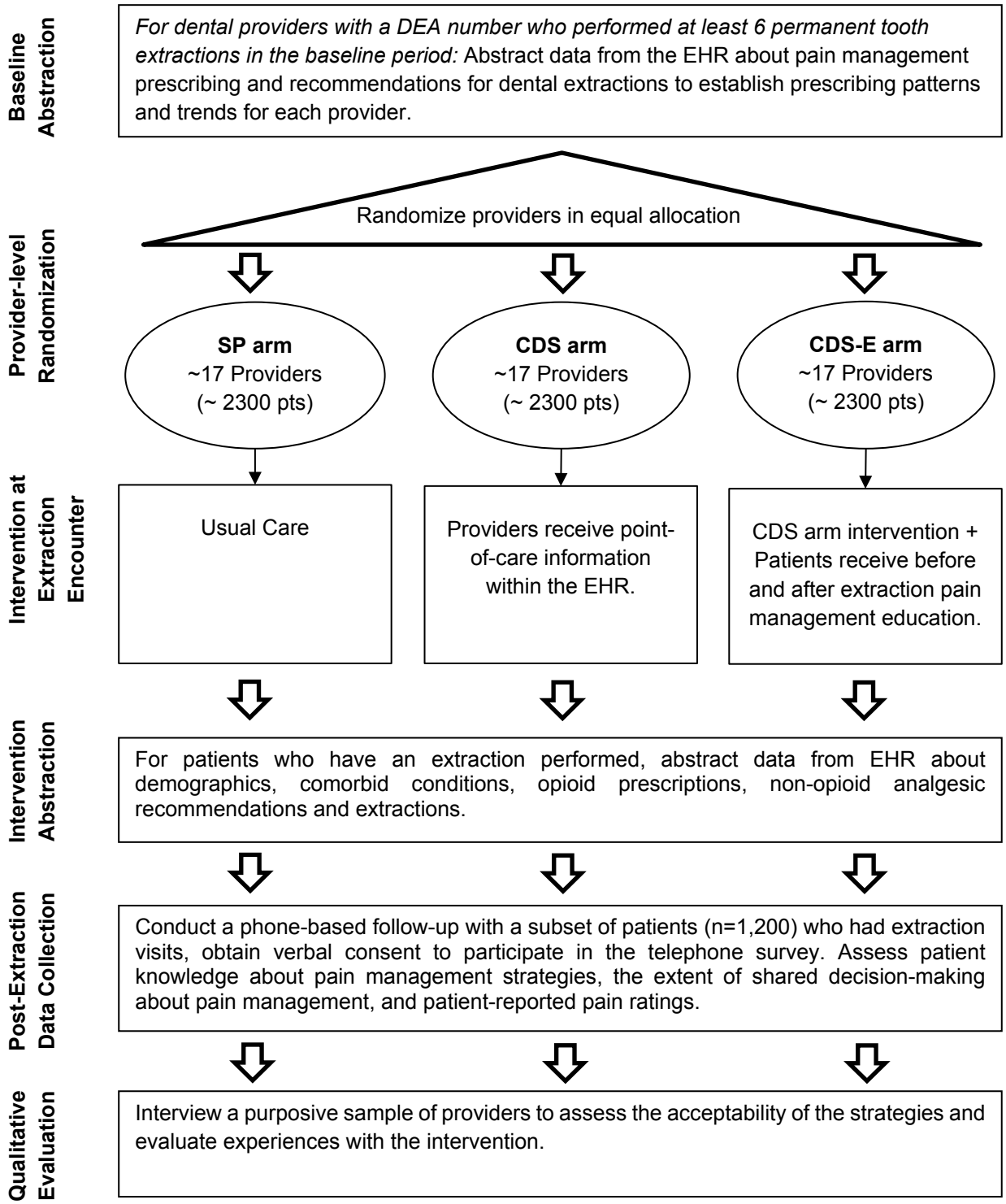
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	De-Implementing Opioid Use and Implementing Optimal Pain Management Following Dental Extractions
Study Description:	The overarching goal of this project is to de-implement the reliance on opioid analgesics and to implement reliance on non-opioid analgesics to manage pain following dental extractions. Using a prospective, 3-arm cluster randomized trial design with dentists as the unit randomized and patient-level prescribing data as the primary outcome, the study team will compare different strategies to reduce the reliance on opioids and increase the use of alternative pain management approaches utilizing information support tools aimed at both providers and their patients.
Objectives:	Primary Objective: (1) To test the efficacy of two interventions (Clinical Decision Support with and without Patient Education), compared to treatment-as-usual to decrease opioid prescribing for dental extractions. Secondary Objectives: (1) To test the efficacy of two interventions (Clinical Decision Support with and without Patient Education), compared to treatment-as-usual to increase exclusive non-opioid pain management for dental extractions. (2) To compare the degree to which each of the 3 study arms (Clinical Decision Support with and without Patient Education, and treatment-as-usual), facilitates shared provider and patient decision-making concerning pain management options for dental extractions. (3) To explore whether the study interventions lead to differences in patient experiences of post-extraction pain.
Endpoints:	Primary Endpoint: (1) Differential pre- to post-intervention change by study arm in the percentage of extraction encounters with an opioid prescribed. Secondary Endpoints: (1) Differential pre- to post-intervention change by study arm in the percentage of extraction encounters at which a provider recommended NSAIDs and/or APAP and did not prescribe opioids at the extraction encounter. (2) Study arm comparison of the mean of the patient-reported shared decision making composite score (composite of 3 components concerning management of post-extraction pain options: effort to explain, to listen, and to personalize) (3) Study arm comparison of the average patient-reported pain in 3-6 days following the extraction.
Study Population:	Providers: Up to 60 (target=51) practicing dental providers at HealthPartners with current Drug Enforcement Agency (DEA) license who performed at least 6 permanent tooth extractions in the baseline period

	Patients: Up to 16,800 [8,400 baseline (target=6,900) and 8,400 intervention (target=6,900)] dental patients age 16 and older, who have a permanent tooth extraction performed by a HealthPartners dental provider who is eligible for the study
Phase:	III
Description of Sites/Facilities Enrolling Participants:	21 HealthPartners dental clinics in Minneapolis- St. Paul metropolitan area
Description of Study Intervention:	Standard Practice: Usual care Clinical Decision Support (CDS): Providers receive point-of-care information within the EHR. Clinical Decision Support plus Education (CDS-E): Providers receive point-of-care information within the EHR and their patients receive before and after extraction pain management education
Study Duration:	48 months
Participant Duration:	Providers: 27 months or 33 months for Providers participating in qualitative follow-up Patients: 1 month

1.2 SCHEMA


Baseline Abstraction
For dental providers with a DEA number who performed at least 6 permanent tooth extractions in the baseline period: Abstract data from the EHR about pain management prescribing and recommendations for dental extractions to establish prescribing patterns and trends for each provider.
Provider-level Randomization
Randomize providers in equal allocation
SP arm
~17 Providers
(~ 2300 pts)
CDS arm
~17 Providers
(~ 2300 pts)
CDS-E arm
~17 Providers
(~ 2300 pts)
Intervention at Extraction Encounter
Usual Care
Providers receive point-of-care information within the EHR.
CDS arm intervention + Patients receive before and after extraction pain management education.
Intervention Abstraction
For patients who have an extraction performed, abstract data from EHR about demographics, comorbid conditions, opioid prescriptions, non-opioid analgesic recommendations and extractions.
Post-Extraction Data Collection
Conduct a phone-based follow-up with a subset of patients (n=1,200) who had extraction visits, obtain verbal consent to participate in the telephone survey. Assess patient knowledge about pain management strategies, the extent of shared decision-making about pain management, and patient-reported pain ratings.
Qualitative Evaluation
Interview a purposive sample of providers to assess the acceptability of the strategies and evaluate experiences with the intervention.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures: Providers	Baseline Abstraction Week 1 – 52	Cluster Randomization with Providers as the Unit Randomized	Intervention	Intervention Abstraction Week 53– 116	Post-Extraction Data Collection Week 53-117	Qualitative Evaluation
Number of extractions performed	X		X	X		
Demographics	X			X		
Provider type	X			X		
Clinic location	X		X	X		
DEA license	X		X	X		
APAP/NSAID recommendations	X		X	X		
Opioid prescribing	X		X	X		
Randomization		X				
Administer intervention			X			
Informed consent						X
Semi-structured interview						X
Procedures: Patients			Extraction encounter Day 0, Week 1-64		Survey call Day 4 (-1 day/+2 days)	
Extraction date			X			
Demographics			X		X	
Comorbid conditions			X			
Patient visit count			X			
Extraction complexity			X			
Informed consent					X	
Patient-reported outcomes					X	

2 INTRODUCTION

2.1 STUDY RATIONALE

The United States is in the midst of an epidemic of prescription drug overdose deaths, with deaths associated with prescription pain relievers of particular concern.[1] Drug overdose has become the second leading cause of accidental death in the United States.[2] Opioids are currently the most commonly prescribed class of medications in the United States.[3] Opioid analgesics are among the most frequently prescribed drugs by dentists.[6] The proposed trial will test the ability CDS elements to support optimal, non-opioid pain management following dental extraction and utilize opioid pain management only when clinically indicated by clinical contraindications for non-opioid analgesics.

2.2 BACKGROUND

The opioid overdose epidemic. The United States is in the midst of an epidemic of prescription drug overdose deaths, with deaths associated with prescription pain relievers of particular concern.[1] Drug overdose has become the second leading cause of accidental death in the United States.[2] Opioids are currently the most commonly prescribed class of medications in the United States.[3] Since 2000, the rate of deaths from drug overdoses has increased 137%, including a 200% increase in the rate of overdose deaths involving opioids (opioid pain relievers and heroin).[4] Inappropriate prescribing of opioids has driven this unprecedented opioid epidemic, and the Centers for Disease Control and Prevention has strongly recommended fundamental changes in prescribing practices in order to address this public health emergency.[5]

Dentists frequently prescribe opioids for pain management following tooth extractions. Opioid analgesics are among the most frequently prescribed drugs by dentists.[6] For example, an estimated 5 million people undergo third-molar extractions in the United States each year, resulting in postoperative pain, swelling, and discomfort, even when surgical complications are not present.[7] The resulting postoperative pain lasts, on average, 3 to 5 days, and a multipronged approach to pain management often includes icing the jaw to reduce swelling, as well as some analgesics for pain relief. Many patients younger than 25 years are introduced to prescription opioids via postoperative dental pain management following third-molar surgery or wisdom tooth extraction.[8] Recent evidence shows that exposure to opioid analgesic prescriptions following dental procedures are increasing over time.[9]

NSAIDs+APAP are an effective alternative to opioids for post-extraction dental pain. Comprehensive reviews concluded that NSAIDs are remarkably effective analgesics for relieving postoperative dental pain and that opioid analgesics have a high incidence of adverse effects.[10-12] Recent evidence concludes that the combination of ibuprofen-acetaminophen provides analgesia that is at least equivalent to that of commonly prescribed opioid combination formulations.[13] Thus, NSAIDs+APAP provides a viable and evidence-based pain management alternative to prescription opioids.[13] Nevertheless, most dental practitioners report that they prescribe opioid medications such as hydrocodone or oxycodone following third-molar extractions.[14,15] Many practitioners appear to underestimate the immediate risks and the long-term harms associated with prescription opioids, even as they overestimate opioids' therapeutic benefits.[16] Strategies to support practitioners in de-implementing their overreliance on prescription opioids following dental extractions in favor of safer alternatives are urgently needed.

The role of the patient in pain management. Self-management skills such as patient education, decision making, and forming a patient-provider partnership have long been associated with chronic disease management[22] but can be effective components of acute pain management as well. While patient-provider shared decision making is considered the preferential choice when no clear treatment option is optimal,[17] involving the patient in the decision process has distinct advantages with respect to medication adherence, as well.[18] Collaborative decision making involving the patient and the dentist holds the potential to increase reliance on non-opioid medications.[19] The study team will utilize this strategy to engage patients in the decision-making process related to the choice of analgesics to manage their pain following dental extractions.

Clinical Decision Support (CDS) integrated in Electronic Health Records (EHRs). A well-designed CDS system can support dentists in providing optimal pain management for patients without resorting to opioids when a safer alternative would suffice. CDS provides pertinent clinical information to the dentist. It can provide evidence-based information and guidance in the form of prompts and reminders to inform clinical decisions about prescriptions. Finally, CDS can offer a mechanism for communicating with patients in the days following the procedure through features such as patient portals and automatic text reminders. In doing so, CDS can enhance education of patients about effective pain management strategies and potentially improve compliance with post-extraction care, resulting in a better experience during the week following the extraction. CDS also provides the advantage of ensuring fidelity of the implementation strategy.

Public Health Impact. This cluster randomized trial with providers as the unit randomized will test the ability of CDS to support the de-implementation of prescription opioids to manage pain following dental extraction and promote the use of NSAIDs+APAP as an effective alternative in patients where this is appropriate. This study is highly significant because it could lead to a CDS tool that could help dental practitioners across the United States decrease their unnecessary prescribing of opioids following tooth extractions, a common dental procedure that affects millions of Americans each year. Public health will be promoted by decreasing the amount of opioids available in the community, which are a source of medication diversion, misuse, and overdose death.

The CDS incorporates novel design features that will save significant time, ensure good fit into the dental care work flow, and facilitate the delivery of personalized care by providing the relevant medical history, informing best treatment decisions, and promoting more evidence-driven pain management following tooth extractions. This proposed implementation project has the potential to drive a major improvement in prescribing practices and the management of pain following tooth extractions in the field of dentistry. As new strategies for pain management are ready to be introduced into clinical practice, they can be readily integrated into this platform in a timely manner.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks to provider participants are considered minimal. Provider prescribing and documentation is a regular part of clinical practice and healthcare delivery. HealthPartners regularly reviews and utilizes this information (e.g., billing and claims). Across all study arms, a potential breach of confidentiality of study data may expose individual provider differences in prescribing and recommendations. To minimize the potential of such a breach of confidentiality, no individually identifying information on provider behaviors collected as part of this research project will be made available in publications or

dissemination efforts. Results that are shared will be in aggregate form. If confidentiality were breached and quality of care were seriously out of range for one or more providers, academic or management leadership could conceivably use this information to the disadvantage of provider. Therefore, no identifying information on individual provider performance with respect to the clinical domains addressed in this study or any other aspect of care gathered as part of this research project will be made available to leaders or managers who make academic, employment, compensation, or disciplinary decisions.

For providers assigned to the CDS or CDS-E arms, the study team expect exposure may shift individual prescribing and/or pain management recommendations following dental extractions. In current dental practice, there is variation with regards to prescribing and pain management recommendations following dental extractions; the study team expects any shift in these behaviors to be within usual care. It is possible, although not intended, that repeat CDS exposure may impact these behaviors for other dental procedures, in that provider communication skills and efficacy may change. To minimize the potential risks associated with changing provider prescribing and/or pain management recommendations, the study team has designed the CDS to promote behaviors consistent with the American Dental Association guidelines and provider training will reiterate.

Potential risks to patient participants are considered minimal. For patients in all study arms, there is a potential breach of privacy of individually identifying study data. To minimize this risk, no individually identifying patient information will be made available in publication or dissemination efforts. Results that are shared will be in aggregate form.

For patients whose providers are exposed to the CDS, there are several additional potential risks. First, the CDS may not display all relevant clinical information about the patient, as the CDS is limited to what is contained in the EHR. Second, it is possible that the CDS could erroneously attribute a condition or drug to a patient based on the EHR. In the design phase, the study team will seek and feedback from multiple sources to ensure that the content and CDS firing is as accurate and appropriate as possible. Before implementation, several investigators will review and test the CDS firing to optimize the information displayed. Provider training will inform providers of these limitations and offer strategies to further minimize these risks. Throughout the implementation phase, the study team will request feedback from providers using the CDS to identify any issues and modify the CDS, if needed.

Third, the CDS may be inappropriate for a given individual patient and, if applied without further checking the clinical status of a given patient, could lead to erroneous therapy, adverse events, disability, or death. However, the clinical recommendations are personalized based on the patient's medical problem list, allergies and current medications. The risk of untoward consequences from such clinical actions is considered minimal. Moreover, this potential risk is routinely present in every clinical encounter in the health care system. Fourth, the potential shift in provider prescribing and/or pain management recommendations may also have unintended consequences on patients' post-procedure pain management. It is possible that this shift could cause under-controlled pain. Providers encounter this in current dental practice and will address it in a similar fashion consistent with the reasonable standard of care.

In addition to their providers being exposed to the CDS, patients in the CDS-E arm will also receive supplemental patient education. To minimize the potential risk that intervention-related materials might conflict with clinical care recommendations, the supplemental patient education materials will not give any specific pain management recommendations. Instead, the patient education materials will

offer information about pain management options and encourage them to talk with the providers. Patients may feel uncomfortable or awkward voicing their preferences about pain management options with their provider. To minimize this potential risk, provider training will address this.

2.3.2 KNOWN POTENTIAL BENEFITS

Opioids are currently the most commonly prescribed class of medications for the treatment of acute pain in the United States. These medications make a significant contribution to our nation's epidemic of overdoses and are a gateway to using other illicit drugs. The primary benefit of reducing the prescribing of opioids when not clinically necessary is reducing the likelihood of these outcomes for at-risk individuals. For providers assigned to SP and their patients, a potential benefit is greater knowledge about whether usual care adequately manages patient-reported pain after a dental extraction, which based on current evidence is unknown.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The implementation of clinical decision support and patient education related to opioid prescribing after a dental extraction poses minimal risk to providers and patients. The CDS does not explicitly make a recommendation about pain management options, but rather facilitates provider access to clinically relevant information. Default messaging are consistent with current American Dental Association practice guidelines, suggesting NSAIDs as a first line treatment for post-extraction dental pain. The CDS display and intervention training will reinforce that pain management prescribing and recommendations should be based on provider judgement. Therefore, patients will be exposed to usual care. The biggest known risk is the potential breach of privacy, for which appropriate measures have been taken to mitigate the possibility of such risk. The potential for these interventions to reduce opioid prescribing among dental providers in terms of dose and number of pills has important public health implications that outweigh the potential risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To test the efficacy of two interventions (Clinical Decision Support with and without Patient Education), compared to treatment-as-usual to decrease opioid prescribing for dental extractions.	Differential pre- to post-intervention change by study arm in the percentage of extraction encounters with an opioid prescribed (during the day of the extraction encounter).	*A prescription is legally required for opioids to be dispensed. Prescriptions are reliably and routinely entered in the electronic health record.*
Secondary		
To test the efficacy of two interventions (Clinical Decision Support with and without Patient Education), compared to treatment-as-usual to increase exclusive non-opioid pain management for dental extractions.	Differential pre- to post-intervention change by study arm in the percentage of extraction encounters at which a provider prescribed or recommended non-opioid analgesics (ibuprofen, naproxen, aspirin, or acetaminophen) and did not prescribe opioids (at the time of the extraction encounter).	*A discrete data element in the electronic health record exists for documenting a non-opioid recommendation. Documentation standards ensure these are routinely documented.*
To compare the degree to which each of the 3 study arms (Clinical Decision Support with and without Patient Education, and treatment-as-usual), facilitates shared provider and patient decision-making concerning pain management options for dental extractions.	Study arm comparison of the mean of the patient-reported shared decision-making composite score (composite of 3 components concerning management of post-extraction pain options: effort to explain, to listen, and to personalize 3-6 days after the extraction encounter)	*Patient report best captures the patient experience of the encounter. This is a modification validated, succinct patient-reported outcome measure used to demonstrate the extent of shared decision making.*
To explore whether the study interventions lead to differences in patient experiences of post-extraction pain.	Study arm comparison of the average patient-reported pain following the extraction (3-6 days after the extraction encounter).	*Patient report best captures pain experience. The Numeric Rating Scale is a validated patient-reported outcome measure used to measure pain level in research and clinical practice.*

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is a prospective, 3-arm, cluster randomized trial (Phase III) in which up to 60 dental providers (accrual goal: n=51) practicing at HealthPartners dental clinics are randomized in a 1:1:1 allocation ratio to either standard practice (SP) or one of two clinical decision support arms (CDS or CDS-E). Patients (up to n=8,400, accrual goal: n=6,900) are exposed to the study arm of their dental provider. Opioid prescribing measured at the patient-level serves as the primary outcome. Opioid prescribing data for patients (up to n=8,400, goal: n=6,900) seen in the baseline period and unexposed to the intervention is utilized in the analysis to examine secular trends in opioid prescribing. Additional outcomes are also measured at the patient-level include: a recommendation or prescription for non-opioid analgesics from the electronic health record and patient reported outcomes about shared decision making and pain identified through surveys.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The cluster-randomized trial design randomizes dental providers to one of three study arms. This design maximizes the number of randomized units (providers) as compared to clinic- level randomization. Cluster randomization with providers as the unit randomized allows for techniques to balance attributes of providers and their patients across study arms. This design also solves the practical issue of providers floating across several clinics and different study arms that would occur in clinic- level randomization. Cluster randomization with providers as the unit randomized also has advantages over patient-level randomization because providers who are exposed to the interventions intermittently may change their usual practices in ways that would not occur naturally. Cluster randomization with providers as the unit randomized also matches the unit of randomization with the level at which the intervention is expected to have an effect, which is at the provider level.

The Standard Practice (SP) arm was selected as a control to reflect care as it is currently performed and to serve as a comparison of secular trends in care, by contrasting such trends in a provider group that does not receive an intervention (SP), with those providers in the two active intervention arms (CDS, CDS-E).

4.3 JUSTIFICATION FOR DOSE

Not applicable

4.4 END OF STUDY DEFINITION

A provider participant is considered to have completed the study if they have completed the intervention period as shown in the Schedule of Activities (SoA), Section 1.3 or they leave employment at HealthPartners. A provider participant will have the option to provide feedback about their experience during the intervention period in a sub-study evaluating the intervention.

For a patient not selected to complete a survey, they are considered to have completed the study when regular dental care for their index extraction encounter is completed as shown in the Schedule of Activities (SoA), Section 1.3.

For a patient participant selected to complete a survey, they are considered to have completed the study after completing the survey call as shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Providers

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Have a current Drug Enforcement Administration (DEA) number allowing them to write prescriptions for controlled substances, including opioids, during the baseline period
- Perform dental extractions of permanent teeth on a regular basis (a minimum of 6 extraction encounters during the baseline period)

Patients

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Have a dental extraction of a permanent teeth performed by an eligible HealthPartners provider during the intervention period

5.2 EXCLUSION CRITERIA

Patients

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients who have opted out of research at HealthPartners
2. Patients under 16 years of age

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

5.4 SCREEN FAILURES

Implementation of the CDS is considered a HealthPartners Dental Group initiative in as a part of their strategy to reduce opioid prescribing. As such, providers are not consented for the study. Providers not eligible for the study will not be included in data collection activities and the data from their patients will not be included in the study. There will be no screen failures for providers.

Patients will not be consented to the study for the primary study objective. Patients not eligible for the study or those who have opted out of research will not be included in the analysis. Patients who provide consent for the survey-based objective are known to be study eligible at the time their consent is requested. There will be no screen failures for patients.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Implementation of the CDS is considered a HealthPartners Dental Group initiative. The project is being implemented with the aim of reducing opioid prescribing. Consent has been provided by dental leadership in accordance with HealthPartners practices.

Providers randomized to the CDS or CDS-E will be exposed to the clinical decision support, integrated into the EHR. Patients who receive care from providers randomized to the CDS-E arm will also be exposed to study-specific patient education.

For the subset of patients eligible to receive a survey, patients will provide verbal consent for survey participation via telephone, which will be obtained by trained survey administrators. If a patient chooses not to participate, another patient will be sampled and called.

Further information about the strategies for recruitment and retention are detailed in the Manual of Procedures.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention will be active within HealthPartners Dental Group for 12 months or until patient accrual goals are met. After completion of the study, the HealthPartners Dental Group will decided whether to continue its activity, but this will be beyond the study's scope.

Standard Practice: Providers will not receive point of care decision support, serving as the control group representing usual care. Patients will receive usual dental care.

CDS: Providers will receive point of care decision support to guide pain management recommendations and prescribing for patients who receive dental extractions. The clinical decision support will highlight: (1) potential medication interactions between the patient's current medications and commonly recommended analgesics for patients following dental extractions; (2) relevant health conditions that may impact pain management strategies; and (3) automated access to the Prescription Drug Monitoring Program. Patients will receive usual dental care [when implemented by HealthPartners Dental Group: access to the Prescription Drug Monitoring Program via the clinical decision support tool will be suspended to align with the organization approach via the electronic health record].

CDS-E: Providers will receive point of care decision support to guide pain management recommendations and prescribing related to dental extractions. The clinical decision support will highlight: (1) potential medication interactions between the patient's current medications and commonly recommended analgesics for patients following dental extractions; (2) relevant health conditions that may impact pain management strategies; and (3) automated access to the Prescription Drug Monitoring Program [when implemented by HealthPartners Dental Group: access to the Prescription Drug Monitoring Program via the clinical decision support tool will be suspended to align with the organization approach via the electronic health record].

In addition, patients will receive an educational handout prior to the extraction procedure comparing effectiveness for managing pain, risks and benefits of non-opioid pain medications and opioid medications. This handout intends to initiate a conversation between the patient and provider about patient needs, goals and preferences. The patient will also receive an education handout about pain management after dental extraction for their reference. This handout intends to normalize the experience of some discomfort and to help patients decide about whether to contact their provider for additional help to manage their pain after extraction. Patients will receive usual dental care.

6.1.2 DOSING AND ADMINISTRATION

Not applicable

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Not applicable

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The randomization of providers to study arm will utilize stratification on baseline factors in order to balance key provider factors evenly across study arms. Specific stratification factors to be utilized will be outlined in the Statistical Analysis Plan. Providers will be randomly allocated 1:1:1 through a computer-generated program to either Standard Practice, CDS, or CDS-E. Patients will be exposed to the intervention to which their provider has been randomized based on the provider they see at the index extraction visit. Systematic sampling with a variable sampling ratio by provider will be used to identify a sample of patients to receive the post-visit survey. This sampling strategy will approximate stratified random sampling and ensure roughly equal counts of patient surveys by provider and study arm. At each patient encounter, the CDS Web service will collect patient level data from the EHR (e.g., medical conditions, current medications, social history). Providers assigned to the CDS or CDS-E arms will be able to access the information using the CDS tool. Providers assigned to the control arm will continue to use their usual methods to assess and address pain management for dental procedures without any effort to influence their prescribing of analgesics following the dental extraction. They will not be shielded from other outside influences.

At the index encounter (the initial patient visit for a dental extraction during the intervention period where all the study criteria are met), the patient is assigned a unique study identifier that is used to link patient encounter data over time. All index and subsequent encounter data for eligible patients are stored in a limited de-identified analysis dataset.

In order to minimize contamination across study arms, only providers in the CDS or CDS-E arms will be able to access the clinical decision support. Similarly, patients who receive care from providers in the CDS-E arm will have access to supplemental patient education. As such, both groups will know their assignment. The study team will not disclose the study's purpose, objectives, or outcomes measures directly to patients until after the encounter or after the participant has been surveyed about their experience, if selected.

6.4 STUDY INTERVENTION COMPLIANCE

The CDS is embedded into the existing EHR. CDS use will be documented to monitor fidelity in the intervention arms. Co-Investigators will regularly meet with study staff to discuss study progress and problem-solve potential issues. The purpose of these meetings is to focus on the day-to-day operations of the project (e.g., technical functionality) and to assure that all necessary tasks are completed in a timely fashion and strictly according to study protocol (e.g., integration into workflow and/or supplemental training). Quarterly meetings will include all co-investigators and will address any scientific issues (e.g., recruitment or enrollment) or safety issues (e.g., medication interactions) that may arise.

6.5 CONCOMITANT THERAPY

Not applicable

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Providers should exercise clinical judgment and can at their discretion disregard any information the CDS offers. As such, patients will receive usual dental care, regardless of study arm.

Hospitalizations documented within the HealthPartners electronic health record that occur within a 72-hour window following the index extraction encounter will be chart reviewed for severity and relatedness on a quarterly basis during the intervention period by Co-investigator and/or PI D. Brad Rindal. These hospitalizations rates will be compared at a frequency determined by the DSMB or quarterly whichever is greater.

Based on the relevant data, the study team in consultation with the DSMB would determine whether the study intervention needed to be modified or discontinued.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Providers

Providers may freely leave employment from HealthPartners. The timing of their employment will impact whether or not they are randomized, whether or not they receive training, whether or not they are exposed to the intervention, and whether or not they are lost to follow-up.

Patients

For the sub-sample of patients who are selected for a survey, patients are free to withdraw from participation in the survey at any time upon request. Patients may wish not to participate for any reason, including due to the perceived impact on their time or privacy. Within the parameters detailed in the MOP, study staff will provide support and encouragement to participants in order to minimize withdrawal and attrition for survey participation. Withdrawal from survey participation will be tracked by the CESR staff in the centralized study database.

7.3 LOST TO FOLLOW-UP

Providers

Providers are considered lost to follow-up if: they do not complete at least 6 extraction encounters in the intervention period. Providers lost to follow-up are not replaced and would be excluded from the analysis.

Patients

Patients are considered lost to follow-up if they meet any of the following criteria: (1) they withdraw from participation in the survey at contact or after completing any portion of the survey; (2) they cannot be reached after all call attempts have been made; (3) they cannot be reached within the defined survey window. Such patients would be excluded from the analysis for survey related objectives. It is anticipated that patients will be lost to follow-up by the nature of survey data collection and sample size selection is made with attention to the anticipated size of this group. If more patients are lost to follow-up than anticipated, additional patients will be sampled.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Primary Objective

To test the efficacy of two interventions (Clinical Decision Support with and without Patient Education), compared to treatment-as-usual to decrease opioid prescribing for dental extractions.

Data source: HealthPartners electronic health record

Procedures:

1. Gather extraction procedure records performed prior to and post CDS implementation
2. Gather opioid medication orders placed within 7 days of extraction procedure
3. Retrieve patient and provider descriptive data

Secondary Objectives

To test the efficacy of two interventions (Clinical Decision Support with and without Patient Education), compared to treatment-as-usual to increase exclusive non-opioid pain management for dental extractions.

Data source: HealthPartners electronic health record

Procedures:

1. Gather extraction procedure records performed prior to and post CDS implementation
2. Gather non-opioid medication recommendations given within 7 days of extraction procedure
3. Gather patient and provider descriptive data

To compare the degree to which each of the 3 study arms (Clinical Decision Support with and without Patient Education, and treatment-as-usual), facilitates shared provider and patient decision-making concerning pain management options for dental extractions.

Data source: Telephone administered patient survey responses

Procedures:

1. CESR staff will administer the survey by telephone
2. CESR staff will input patient responses into RedCap
3. Data will be exported and provided to the statistician

To explore whether the study interventions lead to differences in patient experiences of post-extraction pain. Data source: Patient survey

Procedures:

1. CESR staff will administer the survey by telephone
2. CESR staff will input patient responses into RedCap
3. Data will be exported and provided to the statistician

8.2 SAFETY AND OTHER ASSESSMENTS

The study does not include objectives or endpoints concerning safety. However, the monitoring activities described below will be conducted to assess possible harm.

Identify whether the CDS inappropriately fires or inappropriately offers considerations

Data source: Provider report to alert study team about potential issues or concerns

Procedures:

1. Providers randomized to an intervention arm will be offered training.

2. They will be instructed to notify the study team when clinical judgement differs from the CDS
3. Notification options: (a) Contact Co-Investigator Don Worley or PI D. Brad Rindal; (b) select a "feedback" button contained within the CDS

Identify potential adverse events
Data source: HealthPartners electronic health record
Procedures:
1. Gather hospitalizations, emergency department visits, observational bed, and subsequent opioid prescribing made within 3 days post-extraction procedure

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either of the co-PIs, it results in any of the following outcomes: (1) death, (2) a life-threatening adverse event, (3) inpatient hospitalization or prolongation of existing hospitalization, (4) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or (5) a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related (Possible, Probable, Definite)** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related (Unlikely, Not related)** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

Adverse events will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention. As the intervention for this study is a pain management clinical decision support module, inadequately managed pain, drug interactions or side effects related to pain medications are expected adverse events.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Since there are no routine research contacts for all eligible patient participants, we will collect information from the electronic health record about hospitalizations, emergency department visits, observational bed, and subsequent opioid prescribing made within 3 days post-extraction procedure. This is consistent with the usual care delivery pathways and workflows related to dental procedures.

For the sub-sample of patients reached as part of survey data collection, CESR staff provides information to call their dental provider with questions or concerns. In this manner, the study team will not interfere with existing patient-provider communication, but rather support usual care.

8.3.5 ADVERSE EVENT REPORTING

PI D. Brad Rindal or his designee will report necessary AEs in accordance with HPI Research Subjects Protection Program Standard Operating Procedures at the time of the event. More details about reporting are outlined in the DIODE Data Safety Monitoring Plan.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Any AE considered serious by a dental provider, study investigator, or PI, or which meets the definition of an SAE included in Section 8.3.2, Definition of Serious Adverse Events must be submitted to PI D. Brad Rindal, as soon as possible.

PI D. Brad Rindal or his designee will report necessary SAEs in accordance with HPI Research Subjects Protection Program Standard Operating Procedures at the time of the event. More details about reporting are outlined in the DIODE Data Safety Monitoring Plan.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

Not applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The study team member or dental clinic staff will report unanticipated problems (UPs) to Co-investigator Don Worley or PI D. Brad Rindal. They will submit to Co-investigator Steve Asche to collect and to aggregate. The PI D. Brad Rindal will be responsible for ensuring the assigned Institutional Review Board (IRB) receives notification in accordance with HPI Research Subjects Protection Program Standard Operating Procedures at the time of the event. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to NIDCR within one week of the investigator becoming aware of the event.

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within one month of the IRB's receipt of the report of the problem from the investigator.

All unanticipated problems will be reported to NIDCR's centralized reporting system via Rho Product Safety:

(1) Product Safety Fax Line (US): 1-888-746-3293

(2) Product Safety Fax Line (International): 919-287-3998

(3) Product Safety Email: rho_productsafety@rhoworld.com

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

(1) US: 1-888-746-7231

(2) International: 919-595-6486

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

H1 (alternative): Providers in the CDS and CDS-E strategy arms will reduce their likelihood of prescribing opioids for patients following extractions more than providers in the SP arm.

H1 endpoint: Comparison across study arms of the differential change in percentage of permanent tooth extraction encounters having an associated opioid prescription on the day of the extraction encounter, from the one year prior to the intervention implementation to one year after the intervention implementation.

- Secondary Efficacy Endpoint(s):

H2 (alternative): Providers in the CDS and CDS-E strategy arms will increase their likelihood of prescribing or recommending non-opioid analgesics at the extraction encounter and not prescribing opioids for patients following extractions more than providers in the SP arm.

H2 endpoint: Comparison across study arms of the differential change in percentage of permanent tooth extraction encounters having both 1) a prescription or recommendation in the treatment plan for non-opioid analgesics and 2) to not have an associated opioid prescription on the day of the extraction encounter, from the one year prior to the intervention implementation to one year after the intervention implementation.

H3 (alternative): Patients will report higher levels of the extent of shared decision making in the CDS-E arm than the CDS or SP arms.

H3 endpoint: Comparison across study arms of the mean of the 3-item composite of adapted Collaborate Shared Decision Making score reported by the patient.

H4 (descriptive): Compare patient report of average pain in the week following extraction across the 3 study arms.

H4 endpoint: Comparison across study arms of the mean pain rating in the 3-6 days since the extraction encounter, self-reported by patients.

9.2 SAMPLE SIZE DETERMINATION

- Primary Efficacy Endpoint(s):

H1 (alternative): Providers in the CDS and CDS-E strategy arms will reduce their likelihood of prescribing opioids for patients following extractions more than providers in the SP arm.

H1 patient-level endpoint: A binary code (0/1) indicating that a provider prescribed an opioid medication to the patient on the date of the index extraction encounter.

Sample size and power: Preliminary data from 2018 indicates there will be 6,900 unique patients age 16 and higher with a permanent tooth extracted by 51 dental providers in the baseline period and also an estimated 6,900 unique patients age 16 and higher with a permanent tooth extracted by 51 dental providers during the intervention period. The study analysis is expected to have at least

this many patients. Fully 40% of encounters in the baseline period with patients having a permanent tooth extraction included a prescription for opioid use, and the provider-level opioid use ICC=0.3. Assuming the use of a generalized linear mixed model, with alpha=0.05, two-sided tests , the planned analysis for H1 can detect a differential raw reduction of 23% from pre- to post-intervention opioid prescribing when comparing CDS or CDS-E patients (40% with opioid prescriptions pre-implementation to 15% post-implementation) to SP patients (40% with opioid prescriptions pre-implementation to 38% post-implementation) with 80% power. Power calculations were conducted with PASS v11 (NCSS Software).

- Secondary Efficacy Endpoint(s):

H2 (alternative): Providers in the CDS and CDS-E strategy arms will increase their likelihood of recommending NSAIDs and/or APAP at the extraction encounter and not prescribing opioids for patients following extractions more than providers in the SP arm.

H2 endpoint: A binary code (0/1) indicating that a provider both 1) prescribed or recommended in the treatment plan use of non-opioid analgesics and 2) did not prescribe an opioid prescription on the date of the extraction encounter.

Sample size: This analysis will use the same analytic sample described for H1. The rate is unknown but will be lower than the percentage not prescribing opioids in H1 (60%) since the endpoint is a composite requiring no opioid prescription and also recommendation of non-opioid analgesic.

H3 (alternative): Patients will report higher levels of the extent of shared decision making in the CDS-E arm than the CDS or SP arms.

H3 endpoint: Mean of the 3-item composite of adapted Collaborate Shared Decision Making score reported by the patient within 3-6 days of the extraction encounter.

Sample size: Survey materials will be sent to 1520 patients. The historical response rate for dental research surveys at the organization is 79%, yielding surveys returns from 1200 patients.

H4 (descriptive): Compare patient report of average pain in the week following extraction across the 3 study arms.

H4 endpoint: Mean pain rating in the 3-6 days since the extraction encounter, self-reported by patients within 3-6 days of the extraction encounter.

Samples size: This analysis will use the same analytic sample from the patient survey as described in H3.

9.3 POPULATIONS FOR ANALYSES

Patient Encounter Study Population for H1, H2

The analytic denominator for H1 and H2 will consist of up to 16,800 (8400 baseline and 8400 intervention) first extraction encounters of patients aged 16 and higher and linked to a study-eligible provider, and who have a permanent tooth extraction during the year prior or year after the implementation of the strategies.

Patient Study Population for H3, H4

The analytic denominator for H3 and H4 will start with the approximately 8,400 patients who meet the criteria for the analytic denominator during the intervention period for H1 and H2 above. This analytic dataset will be further reduced to the approximately 1,520 patients who are approached to complete and complete a patient survey within 6 days of the index encounter. Of the approximately 1,520 patients approached it is expected that the analysis for H3 and H4 will include data from 1,200 patients.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Baseline characteristics of study participants will be summarized with mean and standard deviation for interval data and proportions for categorical data. General and generalized linear mixed models will be used to test study arm differences in endpoints. Models will include terms for study arm, time (for models assessing change from pre- to post-intervention), and their interaction. Covariates to be included in models will be described in the Manual of Procedures (MOP). A random intercept for provider will be included in models to account for the cluster-randomized design with providers as the unit randomized. Differential change will be compared for each study arm via a series of planned contrasts. Study arm contrasts will be tested at alpha=0.05 and all tests will be two-sided. Model-predicted means and proportions along with 95% confidence intervals will be used to assess the magnitude, direction, and precision of intervention effects.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

H1: Providers in the CDS and CDS-E strategy arms will reduce their likelihood of prescribing opioids for patients following extractions more than providers in the SP arm.

Analysis plan: Hypothesis H1a posits that patient encounters at which extractions are performed by dental providers in the CDS and CDS-E arms will have a larger reduction in the likelihood of receiving an opioid prescription at the index encounter than patient encounters in the SP arm when comparing independent samples of patient encounters before the implementation to patient encounters following the implementation. A generalized linear mixed-model regression with a logit link and binomial error distribution will be used to test the effects of the implementation strategies. The patient-level endpoint (patient received an opioid prescription at the index encounter) is coded as a binary outcome variable. This endpoint will be predicted by 2 fixed-effects terms for study arm of CDS (CDS vs. SP) and CDS-E (CDS-E vs. SP), year in which the patient has an extraction (post or pre-implementation), and by interaction terms of study arm and year. A random intercept for provider will be included in the model to accommodate the cluster-randomized design with providers as the unit randomized. Additional covariates to be included will be described in the MOP. Model-predicted proportions and confidence intervals of opioid prescribing will be summarized by time and study arm jointly. Contrasts will estimate differential reduction in the endpoint comparing CDS vs. SP and CDS-e vs. SP. This analysis will be conducted on the Intention to Treat Analysis Dataset.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

H2: Providers in the CDS and CDS-E strategy arms will increase their likelihood of satisfying the composite endpoint defined by: 1) prescribing or recommending non-opioid analgesics at the extraction encounter and 2) not prescribing opioids at the index encounter for patients following extractions more than providers in the SP arm.

Analysis plan: Hypothesis H2 posits that patient encounters at which extractions are performed by dental providers in the CDS and CDS-E arms will have a larger increase in the likelihood of receiving a prescription or recommendation for non-opioid analgesics and not prescribing opioid s at the index encounter than patient encounters in the SP arm when comparing independent samples of patient encounters before the implementation to patient encounters following the implementation. The same analytic strategy used for the primary endpoint will be used for this secondary endpoint and will be conducted on the Intention to Treat Analysis Dataset.

H3 (alternative): Patients will report higher levels of the extent of shared decision making in the CDS-E arm than the CDS or SP arms.

Analysis plan: Hypothesis H3 posits that patients will report higher levels of the extent of shared decision making in the CDS-e arm than CDS or SP arms during the strategies implementation time period. A general linear mixed-model regression with an identity link and normal error distribution will be used to test the effects of the implementation strategies. The patient-level endpoint is the score on the 3-item composite of adapted Collaborate Shared Decision Making, and is considered an interval-level variable. This endpoint will be predicted by 2 fixed-effects terms for study arm of CDS (CDS vs. SP) and CDS-E (CDS-E vs. SP). A random intercept for provider will be included in the model. Additional covariates to be included will be described in the MOP. Model-predicted means and confidence intervals for the endpoint will be summarized by study arm. A contrast will estimate the difference in the mean of the endpoint for patients in the CDS-e arm vs. CDS and SP (pooled). This analysis will be conducted on the Intention to Treat Analysis Dataset.

H4 (descriptive): Compare patient report of mean pain in the week following tooth extraction across the 3 study arms.

Analysis plan: This analysis is descriptive, and will comparison across study arms the mean pain rating in the 3-6 days since the extraction encounter, self-reported by patients within 6 days of the extraction encounter. A general linear mixed-model regression with an identity link and normal error distribution will be used to estimate the mean and 95% CI of the pain rating for each study arm. The model will include 2 fixed-effects terms for study arm of CDS (CDS vs. SP) and CDS-E (CDS-E vs. SP). A random intercept for provider will be included in the model. Additional covariates to be included will be described in the MOP. Model-predicted means and confidence intervals for the endpoint will be summarized by study arm. This analysis will be conducted on the subset of the Intention to Treat Analysis Dataset who complete a patient survey.

9.4.4 SAFETY ANALYSES

The study does not include objectives or formal endpoints concerning safety. However, potential harm monitoring activities will be conducted as described in section 8.2, and analysis activities conducted as described below.

Identify whether the CDS inappropriately fires or inappropriately offers considerations

The frequency of notifications and content areas (usability, potential safety, or other) will be summarized by study arm (CDE or CDS-E) and provider type.

Identify potential adverse events

Frequencies, proportions and 95% confidence intervals on proportions of patients having hospitalizations documented in the HealthPartners electronic health record within 72-hours of the extraction encounter deemed as adverse events will be summarized by study arm. The

patient encounter study population for H1 and H2 for patients seen following the implementation of the interventions will be used for this analysis. Events with non-overlapping confidence intervals on the proportions by study arm will prompt the study team to assess diagnostic codes related to the encounters from the electronic health record. Frequencies and proportions of diagnostic codes by study arm will be computed.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The cluster-randomized design of the trial increases the probability of study arm imbalance on patient factors. Baseline patient factors will be summarized and compared across the three study arms using descriptive statistics (mean, SD, median, interquartile range, proportion) and confidence intervals. Results of statistical tests conducted on patient factors by study arm will not be used to inform covariate adjustment. Rather, in a-priori sensitivity analyses the models described in the analysis plan will include patient covariates of age, race, and public pay status.

9.4.6 PLANNED INTERIM ANALYSES

There is no interim analysis planned for ending the study due to futility or efficacy.

9.4.7 SUB-GROUP ANALYSES

Not applicable

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable

9.4.9 EXPLORATORY ANALYSES

Not applicable

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The following consent materials will be submitted with the IRB application: a phone script describing the study intervention, study procedures, and risks are given to the participant for verbal consent (patient participant survey call).

Refer to the *Schedule of Activities* for clarity about timing and study population.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in and answer questions as part of the patient survey. Using an IRB-approved script, CESR staff will explain the research study to the participant and answer any questions that arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be affected if they decline to participate in this study.

In addition to completion of training in practices of standardized telephone-administered survey research, CESR staff are trained in HIPAA and the responsible conduct of research through CITI.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PIs will promptly inform study participants, the IRB, and NIDCR and will provide written notification, including the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the PIs, IRB and/or NIDCR.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the PIs.

All research activities will be conducted in as private a setting as possible.

The Data and Safety Monitoring Board, representatives of HealthPartners IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records, as required.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or NIDCR requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at HealthPartners Institute. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by HealthPartners research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the HealthPartners Institute.

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at HealthPartners Institute. After the study is completed, the de-identified, archived data will be transmitted to and stored at HealthPartners Institute, for use by other researchers including those outside of the study.

When the study is completed, access to study data will be provided through HealthPartners Institute.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Principal Investigator	Medical Monitor
D. Brad Rindal, DDS *Senior Investigator*	*Shannon Gwin Mitchell, PhD* *Senior Research Scientist*	*Kevin McBryde, MD*
HealthPartners Institute	*Friends Research Institute*	*NIH, NIDCR*
8170 33rd Avenue South *Bloomington, MN, 55425*	*1040 Park Avenue, Suite 103,* *Baltimore, MD 21201*	
952-967-5026	*410-837-3977 x238*	
Donald.B.Rindal@HealthPartners.com	*smitchell@friendsresearch.org*	

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise and selected by NIDCR. NIDCR will ensure that members of the DSMB are independent from the study conduct and free of conflict of interest, and/or establish measures to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to NIDCR.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by NIDCR's Clinical Research Operations and Management Support (CROMS) contractor. The monitor will evaluate study processes and documentation based on NIDCR standards and the International Conference on Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP).

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by the CROMS contractor, in collaboration with the NIDCR Office of Clinical Trials and Operations Management (OCTOM) and the NIDCR Program Official. The CMP will specify the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Staff from the CROMS contractor will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the CMP. Documentation of monitoring activities and findings will be provided to the site study team, the study PIs, OCTOM, and the NIDCR. The NIDCR reserves the right to conduct independent audits as necessary.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The Co-PIs will provide overall oversight to quality assurance and quality control. Project managers will support study staff with communicating any potential quality assurance or control issues to the Co-PIs. All Co-investigators will be involved with address scientific issues, including refinement of conceptual models, strategies to streamline and deploy the interventions efficiently and effectively, and strategies to maximize both recruitment and retention of study subjects, as well as methods to assure uniformity and fidelity to intervention protocols and data collection. Study staff will collaborate to create regular reports related to subject accrual and data quality to assess the progress of the clinical study, any relevant safety data, and critical efficacy endpoints and provide recommendations to NIDCR.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

EHR records rely on usual care clinical and administrative data.
All survey data will be reviewed for completeness and entered electronically within the centralized study database. Accuracy and completeness of the data is maximized through alerts and pop-ups if the data is inconsistent or not entered.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained until at least 3 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 15 days working days of identification of the protocol deviation, or within 15 days working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to National Institute of Dental and Craniofacial Research Program Official. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

A limited data set from this study may be requested from other researchers following the completion of the all analyses and related publications described in this protocol by contacting one of the study PIs. The request should include a 1-2 pages summary of the proposed secondary analysis.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The HealthPartners IRB, study leadership, and the National Institute of Dental and Craniofacial Research have established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

ACE	Affiliated Covered Entities
ADL	Activities of Daily Living
AEs	Adverse events / adverse experience
APAP	Acetyl-para-aminopheno (aka paracetamol or acetaminophen)
CDS	Clinical Decision Support
CDS-E	Enhanced Clinical Decision Support
CESR	Center for Evaluation and Survey Research
CFR	Code of Federal Regulations
CITI	Collaborative Institutional Training Initiative
CMP	Clinical Monitoring Plan
CROMS	Clinical Research Operations and Management Support
DEA	Drug Enforcement Administration
DHHS	Department of Health and Human Services
DSMP	Data and Safety Monitoring Plan
DTA	Data Transfer Agreement
DUA	Data Use Agreement
EHR	Electronic Health Record
GCP	Good Clinical Practice
HCAHPS	Hospital Consumer Assessment of Healthcare Providers and Systems
HIPAA	Health Insurance Portability and Accountability Act
HPI	HealthPartners Institute
ICH	International Conference on Harmonisation
ID	Identifier
IRB	Institutional Review Board
MAR	Missing at random
MED	Morphine Equivalent Dose
MI	Multiple imputation
MOP	Manual of Procedures
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
NSAID	Nonsteroidal anti-inflammatory drug
OCTOM	Office of Clinical Trials and Operations Management
OHRP	Office for Human Research Protections
OTC	Over-the-counter
PDMP	Prescription Drug Monitoring Program
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAEs	Serious adverse events
SDM	Shared Decision Making
SoA	Schedule of Activities
SP	Standard Practice
UPs	Unanticipated problems
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	07Mar19	Accepted all tracked changes in protocol development and versioned	
2.0	19Dec19	1.1 Synopsis Study population updated to reflect targeted recruitment numbers 1.2 Schema Aligned the wording with the change described above related to permanent tooth extractions 4.1 Overall design Study population updated to reflect targeted recruitment numbers 8.3.4 Time Period and Frequency for Event Assessment and Follow-Up Includes the visit types described elsewhere.	Consistency
		5.1. Inclusion criteria Changed molars to permanent teeth	Clinical relevance
		8.2 Safety and other assessments Expands safety-related data collection to more visit types, adding emergency department visits, observational bed, and subsequent opioid prescribing	Alignment with DSMB recommendation
		8.4.2 Unanticipated Problem Reporting Non-serious UPs reporting will not be reported in an expedited fashion, so related text deleted.	Alignment with funder requirements
		9.2 Sample size determination Sample size determination updated to reflect targeted recruitment numbers	Alignment between sample size and targeted recruitment
3.0	10Mar20	1.1 Synopsis	Clarified the study population numbers
		4.1 Overall design	Clarified the study population numbers

		6.1 Study Intervention(s) Administration	Noted the change to access the Prescription Drug Monitoring Program via the electronic health record rather than the clinical decision support
		6.3 Measures to Minimize Bias	Clarified the approach taken to balance provider factors
		9.2 Sample Size Determination	Clarified the study population numbers
		9.3 Populations for Analyses	Clarified the study population numbers
4.0	13Apr20	**6.1.1 Study intervention description** Timing of change to PDMP access changed to align with HealthPartners Dental Group planning	Due to COVID-19, Epic Care updates at HealthPartners are on hold until further notice.
		8.3.3.2 Relationship to study intervention Added specification to the definition labels	Recommended by Rho/NIDCR in feedback following Site Initiation Teleconference
		8.3.3.3 Expectedness Revised the definition of expectedness	Recommended by Rho/NIDCR in feedback following Site Initiation Teleconference
		8.3.5 Adverse event reporting Referenced further specification about reporting in separate Data and Safety Monitoring Plan	Consistency across protocol and DSMP
		8.3.6 Serious Adverse Events reporting Referenced further specification about reporting in separate Data and Safety Monitoring Plan	Consistency across protocol and DSMP
5.0	28July20	**6.3 Measures to Minimize Bias: Randomization and Blinding** Clarified patient survey sampling strategy	DSMB recommendation

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