NIH Collaboratory
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Health Care Systems Research Collaboratory

Regulatory/Ethics Consultation Call:

Nonpharmacologic Options in Postoperative Hospital-based and Rehabilitation Pain Management (NOHARM)

Friday, December 20, 2019
Meeting Participants

Joe Ali (Johns Hopkins), Judith Carrithers (Advarra), Andrea Cheville (Mayo Clinic), Jennie Conroy (NIH), John Lantos (Children's Mercy Hospital), David Magnus (Stanford), Stephanie Morain, (Baylor College of Medicine), Pearl O'Rourke (Retired from Partners Health), Marguerite Robinson (Mayo Clinic), Tammy Reece (Duke), Marcel Salive (NIA), Kayte Spector-Bagdady (University of Michigan), Jeremy Sugarman (Johns Hopkins), Jon Tilburt (Mayo Clinic), Wendy Weber (NCCIH), Kevin Weinfurt (Duke), Liz Wing (Duke), Scott Wright (Mayo Clinic)

AGENDA ITEMS	DISCUSSION	ACTION ITEMS

Overview of Demonstration Project	• **Overview:** The NOHARM study aims to change the postoperative pain care paradigm to help curb the opioid epidemic. The goal is to encourage use of less harmful nonpharmacologic pain care while minimizing symptoms, preserving patient function, honoring patient values, and maintaining availability of opioids as a last resort. The study will use the electronic health record (EHR) to advance a consistent narrative about nonpharmacologic options and promote and honor patient preferences in pain management.
	
	• **Collaborative network partners:** Four Mayo Clinic–affiliated health systems spanning five states:
	
	    ○ Rochester, Minnesota (MCR)
	
	    ○ Florida (MCF)
	
	    ○ Arizona (MCA)
	
	    ○ Upper Midwest Health System, Iowa/Wisconsin (MCHS)
	
	• **NIH Institute:** National Institute on Aging (NIA)
	
	• **Study design:** NOHARM is planned as a stepped-wedge, cluster-randomized trial testing a bundled Epic EHR-based intervention (including a conversation guide and clinical decision support) to elicit preferences for, document, and point patients toward evidence-based nonpharmacologic pain care for post-hospital, post-surgical pain. It will be implemented in the largest surgical	

Note: These minutes were circulated to all participants on the call for two rounds of review and reflect all corrections that were received.

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	practice areas within the participating health systems. The team has developed a prototype conversation guide to help facilitate better conversations between providers and patients about chronic pain management in ambulatory settings. In the UG3 phase, the goal is to pilot and confirm the functionality of all NOHARM bundle components, data collection procedures, and analytic strategies. In the UH3 phase, the intervention will be randomized sequentially among 18 practice clusters at 6-month intervals and will enroll up to 140,000 patients. Eligible surgeries include transtibial or transfemoral amputations, ankle or knee disarticulations, knee or hip arthroplasties, scheduled C-sections, gynecological surgeries, and colorectal surgeries. These surgeries were selected based on surgical volume and post-operative pain. The study team noted that they now have additional information on surgical volume and are in the process of modifying the inclusion criteria to ensure sufficient study enrollment. • There was a question on the call about the choice of stepped-wedge design. The study team stated that this design was considered ideal for operational reasons and because multiple practices eventually want access to the intervention. However, after consulting with the Collaboratory's Biostatistics and Study Design Core, the team stated that a phased rollout of a parallel design could be an option, and this is still under consideration. • **Primary and secondary outcomes:** The primary outcome is a composite of pain plus function. The team will measure a broad range of outcomes relevant to diverse decision makers, including opioid use, patient-reported outcome (PRO) measures, nonpharmacologic pain care (NPCC) use, healthcare utilization, and process measures. • The team is not collecting data on nonprescription drug use independent of the EHR. • Those on the call asked about a potential issue concerning the inclusion of research data in the EHR (see Issues beyond the study below).	
Status of IRB approval	• The single IRB of record is the Mayo Clinic IRB for both the UG3 and UH3 phases. • The status of phased IRB approvals is:	

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	○ Patient-facing intervention formative data and prototyping activities at the Rochester, MN, site (approved September 2019)
	   ○ Review preparatory to research (approved November 2019)
	   ○ The team expects to submit a prospective intervention pilot at multiple sites to the IRB in mid-February
	   ○ Plan to submit full multisite trial to the IRB in May 2020	

Risk classification	• There are burdens associated with eliciting and documenting patient preferences about nonpharmacologic care. • With respect to risk, there was discussion about the effects of the intervention in reducing opioid prescribing. • Those on the call thought that the NOHARM intervention would be deemed minimal risk because its purpose is to change physician behavior toward guideline-concordant practice. The intervention is not testing the guidelines, but rather whether following the guidelines reduces opioid prescribing while maintaining postoperative function and mitigating pain. • It was pointed out that guidelines from the National Academy of Medicine and the CDC (and others) indicate that opioids should be the last resort for pain, including postoperative acute pain. Guideline-concordant care should be a realistic option within existing delivery systems.	
Consent	• The approach to consent or other approaches to notification and authorization has not been decided yet by the study team. • There was discussion regarding that patient receptivity to the NPPC modality may be different after opioids are withdrawn and they are seeking care options. • This is a population-based study, and the study team hopes to have all eligible patients (who have qualifying surgeries) enrolled. The study team does not want patients to opt out before engaging in conversation as specified in the guide because they will not necessarily have the opportunity to communicate their preferred NPPC modality. • Those on the call discussed that the study team might be able to make the case for a waiver of consent because the study appears to be minimal risk and consent would be impracticable to obtain given the stepped-wedge design if it	

AGENDA ITEMS	DISCUSSION	ACTION ITEMS
	is selected and the nature of the intervention. The study team was encouraged to think about it more and can engage the Core again for further guidance. • There was a suggestion that the team should consider whether the clinicians are participants, because the study will collect information on clinician opioid-prescribing. The study team mentioned that they believed that the care team will not be at risk and can choose not to engage with the intervention. • The Mayo Clinic health system in Rochester, MN, has a special opt-out policy. Based on the Minnesota statute requiring research authorization: Data collected from patients who have not given permission for use of their EHR data for research will not be utilized in the NOHARM trial analyses, reported on, or transferred to the PRISM Centers or outside institutions.	
Privacy/HIPAA	• From the team's supplementary material: Delivery of the intervention will include pain and anxiety monitoring via secure mechanisms and involvement of the study participant's surgical team. All exchanges of clinical information will comply with HIPAA standards of patient privacy, and all data collected, transferred, and stored for research purposes will be done in a manner to assure confidentiality.	Tammy sent the link for the HEAL Initiative's data sharing policy to those on the call (completed December 20, 2019): NIH HEAL Initiative Public Access and Data Sharing Policy: https://heal.nih.gov/about/public-access-data
Monitoring and oversight	• To be determined. The NIA policy requires a 3-5 member DSMB to review the protocol up front and to review progress and safety issues periodically. The study team will confer with NIA to meet the requirements for monitoring and oversight. • DSMBs may still be used when the intervention is minimal risk, especially for large trials.	
Issues beyond the study	• A certificate of confidentiality will be automatically provided per recent NIH policy. This certificate adds provisions for future research uses and confidentiality obligations for future data sharing.	

AGENDA ITEMS	DISCUSSION	ACTION ITEMS
	• The certificate has implications for sharing the dataset later if research data is added to the clinical record because the clinical record may then be considered as part of the research record.	

A. SIGNIFICANCE

<u>Scientific Premise:</u> Perioperative opioid prescribing contributes substantially to the opioid epidemic yet, absent effective alternatives, restricting opioids alone could harm patient outcomes. The ***N**on-pharmacological **O**ptions in postoperative **H**ospital-based **A**nd **R**ehabilitation pain **M**anagement (NOHARM) pragmatic clinical trial* rests on the <u>scientific premise</u> that leveraging existing system tools to better align care with guideline recommendations can not only promote effective, patient-centered, non-pharmacological pain care (NPPC) during the high stakes perioperative interval and curb non-beneficial opioid use, but also enhance outcomes.

More than 180 million legal opioid prescriptions are dispensed in the US each year with a mean dose of over 45 morphine milligram equivalents.[19] Approximately 65% were initiated for the clinical management of acute pain but at some point recipients' consumption converted to unintended, prolonged opioid use (UPOU).[19,20] The most prevalent instance of this pernicious conversion stems from pain management following the over 100 million procedures performed annually in the US.[1] Reports indicate that up to 15% of those exposed to opioids after a procedure, go on to chronic use.[21-28] Conversions to UPOU flood society with excess supply ripe for chronic dependence, addiction, diversion, and lethal overdoses; all projected to increase in the coming decade.[29]
through diversion, and 40-50% use leftover pills from family or friends.[30-32]

Perioperative pain control is crucial to strong clinical outcomes, and opioids play a role in the acute setting. Yet, they should be used sparingly, and only as second or third line agents in the subacute period. Guidelines now consistently incorporate evidence demonstrating that non-pharmacologic pain care (NPPC), including rehabilitative and complementary health approaches (CHAs), should be first line therapies with demonstrated effectiveness and more favorable risk benefit ratio.[9-12] Too often, however, these modalities are only explored if patients and families ask,[15,33] or as a last resort. *Despite the importance of NPPC and its established role in current guidelines, to our knowledge, no pragmatic studies have tested its systematic integration into workflows to enhance postoperative pain while curbing population rates of conversion to UPOU.*

The perioperative care trajectory is a high stakes period during which large volumes of opioids are prescribed, disseminated, and used. This interval offers a sequence of standardized touchpoints and routine structures that can be targeted by system interventions to make "the right thing the easy thing" consistent with medicine's "first do no harm" ethic. The electronic health record (EHR) centralizes surgical workflows and may effectively promote guideline concordance.[34,35] As such, EHRs offer an unparalleled opportunity to influence patient and clinician behavior. Patient preferences and clinician prescribing determine whether opioids or safer NPPC modalities are the default for managing perioperative pain. Through prompts, nudges, and data entry requirements, the EHR can consistently position evidence-based NPPC as a viable first-line option, thereby changing the paradigm of perioperative pain management in a manner that benefits patients and public health.

NOHARM's significance lies in its potential broad reach and dissemination. A bundle of ubiquitous EHR functionality with a portal-embedded NPPC conversation guide (CG) offers a simple, inexpensive, and sustainable healthcare system (HCS) implementation model. We have integrated and pilot-tested the validated components of this pragmatic bundle that could dramatically curb patients' conversion to UPOU through EHR clinical decision support (CDS) that promotes preference-sensitive, guideline-concordant NPPCs at defined touchpoints. While CDS tools are increasingly EHR agonistic, our use of Epic will facilitate dissemination as it is the most common EHR in the US.[36,37]

This trial will occur in 4 semi-autonomous geographically and demographically distinct Mayo Clinic (MC) HCSs across the US. NOHARM will include representative surgical procedures that are associated with disability;[38] NPPC-responsive somatic, visceral and neuropathic pain; and the highest and most variable rates of opioid prescribing.[39,40] NOHARM will promote NPPC therapies that include diverse classes (physical modalities,[41-64] mind-body,[65-82] touch,[83-89] and exercise,[60,90-92]) and delivery modes; are supported by <u>Level I evidence in reducing pain after surgery</u> (**Table 1**); and are accessible, being either self-administered, available at community centers, or covered by insurers. Last, our proposed cohort will allow us to include ~140K participants, thereby enabling us to examine barriers and facilitators to NOHARM bundle effectiveness and heterogeneity across subgroups, with attention to patients at high risk of UPOU.

Class	Therapies	Acute pain S/M*	Acute pain Trial	Opioid reduction S/M*	Opioid reduction Trial	NOHARM surgery S/M*	NOHARM surgery Trial
Physical Modalities	Electrical stimulation, Thermal agents, Compression, Kinesio taping	15	10	7	6	5	5
Mind-body	Music listening, Relaxation, Breathing, Mindfulness	14	3	8	2	6	0
Touch	Reiki, Massage	4	4	2	0	1	0
Exercise	Conditioning, Resistive, Yoga, Tai Chi	3	1	2	1	1	1

Table 1. Number/type of application citations for NOHARM NPPC classes
*Systematic review/meta-analysis - S/M

B. INNOVATION

Promoting uptake of safe, evidence-based NPPC as a viable opioid alternative in perioperative care is crucial to stemming the opioid epidemic. NOHARM applies state-of-the-art thinking about opioid misuse; individualized, CG-elicited, EHR nudges, with user-centered design principles to produce a scalable, bundled intervention within usual care. The proposed work's innovation rests on several NOHARM features:

Embedding conversation support within the EHR. The CG will convert elicited patient NPPC values and preferences into discrete EHR data elements that can trigger workflows, CDS, and user interfaces to shape care in a manner that promotes preferred NPPC. Reaching out to patients via their portals to capture preferences, then amplifying those preferences to reverberate throughout the EHR via CDS will individualize pain management in a manner that is both more guideline concordant and patient-centric.

Leveraging the EHRs' internal logic and patient portal-based outreach capabilities to progressively advance a cohesive narrative through sequential patient touchpoints and different clinical stakeholders. This approach will encourage a.) avoidance of inappropriate, harmful opioid use; b.) adoption of safe NPPCs with more favorable risk benefit ratios; and c.) focusing of human resources on patients at risk for poor outcomes. The strategic, EHR-directed injection of content into sequential touchpoints along the perioperative trajectory will influence conversations and choices that occur at ascertainable points in perioperative care.

Using an individualized, treat-to-target approach that tactically combines patient-elicited preference data with CDS for patient-specific messaging and ordering. Patients' NPPC-related experiences, responses, and receptivity vary widely,[14] as does the spectrum of NPPC modalities. Our approach will tailor prompts, orders, questions, flowsheets, etc. that appear on EHR interfaces to sync with a patient's priorities and needs using Epic's robust data triangulation capabilities that integrate patients' demographic, clinical, and UPOU risk data with their evolving NPPC preferences. Use of these dynamic data sources will enable tailored selection and titration of NPPC based on a patient's clinical response and evolving preferences, rather than standard default opioid prescribing. For example, a patient's residential geocodes can help push local NPPC resources to their portals, and their preferred NPPC modalities, e.g., music therapy and e-stimulation, will auto-populate physical therapy (PT) and nursing orders. This pragmatic approach more closely mirrors real-world practice which tailors evidence-based treatments to patient-specific outcomes and receptivity.[93-97]

Deploying and iteratively refining behavioral economics and screening strategies to address the needs of patients at risk for poor outcomes. The NOHARM intervention seeks to lessen postoperative pain of all patients, however those at risk for UPOU, chronic pain, and disability are its principal targets. By linking patient reported outcome (PRO)-based screening for misuse, negative affect, and functional decline with opioid refill requests (§C.7.iii.), the intervention will discourage prescribing for patients who lack acute need, but will also gather and deploy critical information to clinicians enabling them to offer the best treatments, e.g., referral to a PT, pain clinic, or masseuse. By collecting the information that clinicians require to appropriately prescribe opioid alternatives for patients via the portal, the NOHARM intervention will render ordering of needs-matched, non-opioid treatments easier and more intuitive. Moreover, understanding which intervention components are most used and usable by patients at increased risk of UPOU is a crucial implementation question readily answerable with variables captured in the Epic EHR metadata and further elucidated with qualitative inquiry (§C.9.). Establishing accurate associations between clinicians' use of specific EHR CDS tools and NPPC uptake will provide vital understanding to inform future refinement and implementation efforts.

C. APPROACH

C.1. Background and Preliminary Work
Our team has established foundational elements of the proposed trial in key areas:

Prolonged and Perioperative Opioid Use: Drs. Habermann (co-I), Cima (co-I), Gazelcka (co-I), and Dowdy (co-I) have developed and reported on postoperative opioid prescribing guidelines,[98] and described the persistence of wide variations and over prescription of opioids after surgery,[39,40] including gynecological procedures.[99] Drs. Hooten (co-I) and Tilburt (co-PI) proposed the first empirically-based conceptual framework (§C.2) to account for the complex interplay of factors that lead to UPOU.[20]

Shared Decision Making and CGs: Drs. Tilburt and Leppin (co-I) have written extensively on pragmatic considerations in CGs,[100-103] including CAM-related deliberations and modalities,[104,105] which critically informed Tilburt's comparative effectiveness trial of decision aids in racially diverse populations with early stage prostate cancer.[106] Dr. Tilburt's participation as co-I and site-PI of the NIA-funded UG3/UH3 pragmatic trial to improve advance care planning in HCS gives him relevant experience in implementing timelines for this mechanism.

NPPC effectiveness and Implementation: Team members have contributed to clinical trial-based NPPC effect size estimates including Dr. Chlan's (co-I) work on music therapy;[107] Dr. Cheville's (co-PI) work in yoga,[108] pilates,[109] resistive exercise,[110-112] manual lymphatic drainage,[113,114] and compression;[114] and Dr. Basford's (co-I) work in electromagnetic modalities,[115-117] pilates,[118]
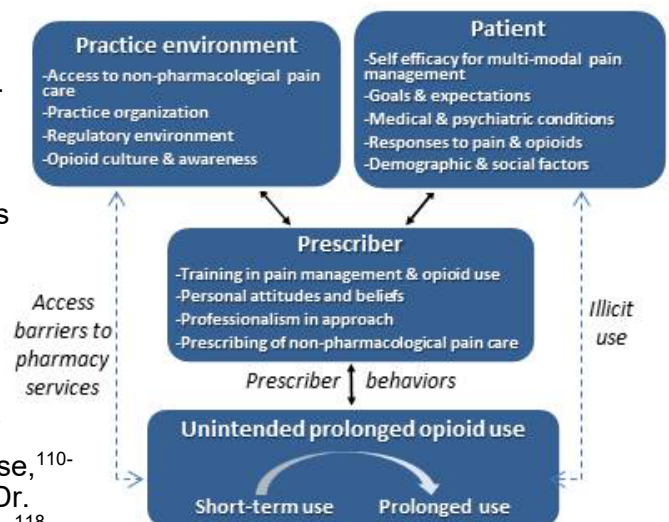

Figure 1. *Hooten et al Mayo Clinic Proceedings* 2017.

and sauna bathing.[119] Drs. Leppin and Tilburt reported the absence of NPPC-related conversations in medical oncology encounters,[15] a finding noted in perioperative cohorts.[33]

EHR Decision support: Dr. Cheville is a multiply certified Epic Physician Builder and PI of an ongoing NCI Moonshot-funded pragmatic clinical trial that leverages Epic EHR CDS to increase appropriate clinical responses to PRO symptom reporting. Dr. Mann (Consultant), an EHR usability expert, currently tests behavioral economics-based EHR promotion of guideline-concordant care (R21AG057382).

Remote optimization of anxiety and function: Drs. Cheville and Kroenke (consultant) validated remote, cost-effective approaches to managing anxiety, disablement, and pain.[120-123] The NOHARM bundle will incorporate these approaches to address pain and anxiety, which potentiate UPOU,[124] and poor function recovery.[125,126]

Our team's participation in opioid stewardship, surgical, and EHR governance for <u>all 4 HCSs</u> will be vital to NOHARM implementation: Drs. Gazelka, Habermann, and Cima lead the Opioid Stewardship Committee; Drs. Habermann and Cima direct Surgical Outcomes in Mayo's Kern Center for the Science of Health Care Delivery (CSHCD); Drs. Cima, Dowdy, and Abdel hold leadership roles on the relevant Surgical Specialty Councils, and Dr. Cima is Vice-Chair of the Surgical and Procedural Committee; Dr. Chlan serves in Nursing Administration; and Dr. Cheville leads an Enterprise PRO Task Force and thereby oversees portal-based PRO data collection.

C.2. Conceptual Model

Our choice of this conceptual model (**Figure 1**) is deliberate. This model is clinical and pragmatic without ignoring important contextual and policy elements that influence UPOU (e.g. practice organization, regulatory environment). It also allows for hypothesis driven examination of patients at high risk of UPOU (Aim 3).[20] The model draws from the well-established *Theory of Unpleasant Symptoms*[127] in identifying factors amenable to modification through the NOHARM's targeting of key touchpoints.

The *Theory of Unpleasant Symptoms* recognizes the critical importance of: 1) co-occurring symptoms; 2) antecedents to the symptom experience; and 3) disablement from uncontrolled symptoms. Consistent with this theory, clinical guidelines,[9] and our previous work, co-occurring anxiety will exacerbate some patients' perioperative pain, increase their opioid consumption, and degrade surgical outcomes. Anxiety therefore represents important therapeutic target that responds to many NOHARM NPPC modalities, e.g. music listening.[125,128,129]

Figure 2.

C.3. Participating Health Care Systems

NOHARM will take place in 4 semi-autonomous HCSs within one national organization that utilizes a unified Epic EHR. The conventionally intense EHR oversight and build regulation in high-volume HCSs render the completion of the required NOHARM EHR build approvals, specifications, and piloting within the 1-year UG3 interval unfeasible in separate HCSs with distinct EHRs.

The NOHARM trial will be conducted in the surgical practices of the MC Rochester (MCR), MC Florida (MCF), MC Arizona (MCA), and MC Upper Midwest Health System (MCHS) (**Figure 2**) which are described in detail in Facilities 9.1-3. These practices span five states, but have broad catchment areas that extend into >10 additional states; over 30% of the MCR surgical patients reside in IL, ND, SD, NE, OH, MI, and IN. Collectively, the HCSs' geographic breadth offers profound diversity with respect to opioid prescribing oversight, insurance coverage, patient demographics, NPPC penetrance, pharmacy stock, post-acute care management patterns and facilities, and population density (~50% of MCHS patients reside US Census Bureau designated rural areas). MC sites encompass representative practice settings. The MCHS includes community hospitals in WI, MN, and IA with surgical services delivered by generalists, while MCR is a high-volume, specialty center with surgeons performing a limited range of high frequencies procedures.

C.4. Overview of Approach

This application proposes a pragmatic, cluster-randomized, population-based clinical trial that will rigorously assess whether a CG-EHR bundle; a conversation guide plus EHR CDS and patient portal reminders/supports deployed at key points on the perioperative care trajectory, improves pain outcomes, and adds value to the utilization of the nation's health care resources. In a 1-year milestone-driven planning phase (UG3), we will confirm the functionality of all NOHARM bundle components, data collection procedures, and analytic strategies (Aim 1). In the subsequent three years, the trial's stepped wedge design (**Figure 3**) will randomize the order of
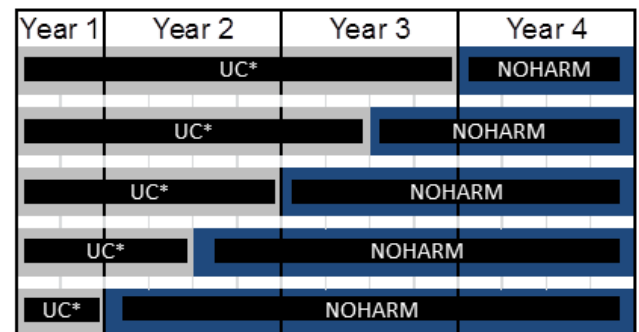

Figure 3. NOHARM Stepped Wedge, UC* - Usual Care comparator

NOHARM implementation among 18 practice clusters in four distinct HCS at staggered 6 month intervals. Roughly 140K patients will be sequentially enrolled. Data will be collected from all clusters for a minimum of 6 months during pre-NOHARM usual care, and 12 months following NOHARM implementation, and analyzed in year 5. Consistent with the goals of our pragmatic trial, we will measure a broad range of outcomes relevant to diverse decision makers including opioid consumption; Patient Reported Outcome Medical Information System (PROMIS) computer adaptive test (CAT) pain intensity, anxiety, and physical function scores; and healthcare utilization at 3 months after surgery (Aim 2). We will additionally collect process measures to assess CDS and NPPC uptake and effectiveness. In parallel, we will conduct a mixed methods study to identify facilitators and barriers to NOHARM bundle implementation and effectiveness among patients at high risk of UPOU (Aim 3).

C.5. Population

Enrollment. This is a population based study, where all eligible patients undergoing transtibial or transfemoral amputation; ankle or knee disarticulation; knee or hip arthroplasty (both primary and revision); C-section; gynecological surgery; or colorectal surgery at a MC HCS will be enrolled. NOHARM will be sequentially implemented across the MCR, MCA, MCF, and MCHS practices, as per the stepped wedge allocation, and will include the roughly 140K patients with qualifying surgeries who will be managed by these practices during 3.5 years of data collection. This inclusive enrollment approach substantially increases the generalizability and external validity of our real-world pragmatic trial.

Characteristics. Roughly 40K patients undergo qualifying surgeries at MC facilities annually; 50% at MCR, 25% within MCHS, and 25% at MCA and MCF combined (**Table 2**) with 18% covered by Medicaid, comparable to national rates,[130] Each HCS' study population's ethnic and racial characteristics reflect their locations. The MCR and MCHS practices are representative of the upper Midwest, excepting higher inclusion of Native Americans, ~3.8%. The MCA and MCF surgical practices serve higher proportions of racial and ethnic minorities that are comparable AZ and FL populations, respectively. We estimate that ~28.7% of study participants will be non-Caucasian, and 65% will be women. 82% of MC surgical patients have portal accounts.

Transparency and Institutional Review. NOHARM qualifies as "standard of care" research in which the primary research objective is to evaluate a strategy that better satisfies the existing standard of care. The Mayo Clinic IRB, that covers all four HCS, has been an active partner in developing the NOHARM application and "*Transparency Promotion and Patient Preference Protection Plan.*" (Human Subjects §3.1) [131-133]

Site	Overall	Amputation	Colorectal	Gynecology	Arthroplasty
Arizona	5823 (15.0%)	58 (10.3%)	593 (13.3%)	3326 (17.0%)	1846 (13.0%)
Florida	4832 (12.5%)	73 (13.0%)	577 (12.9%)	2201 (11.2%)	1981 (14.0%)
MCHS	9969 (25.7%)	128 (22.8%)	718 (16.1%)	4677 (23.9%)	4446 (31.3%)
Rochester	18179 (46.8%)	303 (53.9%)	2585 (57.8%)	9375 (47.9%)	5916 (41.7%)

Table 2. 2018 Surgical Volumes by Specialty & Site in 4 MC Semi-Autonomous HCSs

C.6. Data Capture and Characteristics

Data, excepting Aim 3 qualitative data, will be electronically abstracted either directly from the Epic EHR, or from the MC Unified Data Platform (UDP) which houses aggregated clinical, operational, and administrative data from the MC HCSs. We emphasize outcomes that can be captured with passive follow-up through collection in routine care or established monitoring programs. PRO data; e.g., self-reported oral morphine equivalents (OMEs), will be captured via the portal. Portal-based PRO administration will be integrated with an established surgical outcome monitoring program. Initially confined to the MC Total Joint Registry,[134] the system extends to other procedures to meet state and certifying organization mandates. Response rates are 86% at 3- and 79% at 6-months following surgery. Some state Prescription Drug Monitoring Programs will not release aggregate patient-level data. We will therefore rely on EHR and validated self-report data for OMEs.

Patient characteristics will include sociodemographic (age, sex/gender, race, ethnicity, zip code, insurance) and clinical variables (surgery type, complications, ICU transfer, comorbidities, and medications) and will be automatically abstracted. Validated natural language processing algorithms developed by Dr. Liu (co-I) will be used to ascertain unstructured covariates, e.g., somatization.[135,136] Surgeon and allied health characteristics will, in addition to demographics and practice location, include discipline, total years in practice and % effort spent in clinical practice. Site level data will include setting, available on-site NPPC and rehabilitation services, location, and annual surgical volume and procedural diversity.

C.7. Specific Aim 1. To confirm the feasibility of each component of the NOHARM research strategy.

Subaim 1a: to revise and confirm feasibility & acceptability of a prototype conversation guide.
Subaim 1b: to specify Epic CDS build components with iterative enhancement based on usability testing.
Subaim 1c: to pilot all components of data collection, and EHR components of our bundled intervention.

C.7.i. Aim Overview. In this aim we will confirm all aspects of our bundled, system-based intervention by refining a CG through iterative prototyping, specifying and testing CDS, and piloting at all 4 study HCS.

C.7.ii. Subaim 1a
Our Prototype. Our prototype CG was developed to help facilitate better conversations about chronic pain management in ambulatory settings. Foundational work indicates acceptability and effectiveness in: 1)

Encouraging realistic expectations regarding pain relief, 2) Apprising patients of opioid harms and UPOU, and 3) Introducing evidence-based NPPC. Excellent stakeholder engagement has characterized our foundational work, and accords with reports attesting high clinician uptake and improved communication with shared decision making in pain-related encounters.[17,137-139]

NOHARM adaptations to the primary care CG were informed by focus groups; 3 with clinical and 2 with patient stakeholders. The current NOHARM prototype includes an informational video (**Figure 4.a**), preference elicitation exercise (**Figure 4.b**), and pain management preference grid (**Figure 4.c**) containing links to NPPC information and instruction. The video portion of the CG is brief and has separate sections for easy reference. The preference elicitation exercise queries patients about their NPPC interest, experiences, and past responses, as well as access and cost concerns. Consistent with our user-centered design approach the grid succinctly lists options, relative pain relief, cost, side effects, risk of dependency, and effects on resuming regular activities.

Although the literature suggests that decision support tools help patients see their options more clearly and have better conversations with their care teams,[140,141,142] they show modest efficacy as stand-alone interventions unless they are implemented within workflows and systems. Therefore, we will convert patients' CG-elicited NPPC preferences into discrete EHR data elements, and thereby strategically influence perioperative workflows to promote NPPC uptake. The CG will serve as a familiar common ground that patients can return to repeatedly with different clinicians as they traverse perioperative touchpoints (**Figure 5**) in order to accurately and efficiently communicate their NPPC preferences. The grid (**Figure 4.c**) will provide NPPC information via embedded videos and hyperlinks in one convenient location. The grid will be accessible to clinicians via the EHR, enabling them to discuss viable NPPC alternatives with patients who solicit opioid refills or dose escalations, or have poorly controlled pain.

Prototype Revision. Using the literature on promising conversational interventions, and the existing evidence for NPPC, with patients and clinicians we will iteratively prototype a next version of this CG in a 3-step process. Our user-centered design process creates, develops, and assesses interventions to help end-user's life and work in real life situations.[143] It observes experience and iteratively refines candidate interventions as end-users test them. This approach has been well validated in the development of in shared decision-making tools that increase patient engagement and positively impact clinical outcomes.[144-146]

Step 1. Preparation. A designer will shadow 3 patients in each of the surgical areas at each of our 4 locations (36 total) including at least two points on the perioperative continuum for immersion in the care (provider/patient) experience and audio-recording any conversations with clinicians. Then, the designer and a co-investigator will ask, "what is happening when patients and clinicians, individually or jointly discuss pain in the perioperative period?"; "how does consideration of NPPC contribute to, or fail to contribute to, these conversations?," "what are the barriers to appropriate shared consideration and integration of NPPC?," and "how can conversations

Figure 4.a.

Figure 4.c.

about perioperative NPPC be better supported?" We will discuss those observations in bi-weekly team meetings over a 10-week period (8 sessions). This will provide a pre-intervention context against which to make design judgments as to what might be improved, what improvements might be, and how to adapt successful prototypes in step 2.

Step 2. Prototype Adaptation. Ideas generated in step 1 will be used to adapt the current prototype for evaluation and refinement. The revised prototype will be used in at least 4 clinical interactions with 6 clinicians (24 patient interactions) at three points on the perioperative care continuum. The pre-op surgical visit, the immediate post-op, and post-op discharge information. At each of these points we will conduct debriefing interviews with at least 12 patients and all 6 clinicians to assess self-reported *acceptability, appropriateness, feasibility and sustainability* as measured from 1-10 on a visual analogous scale by both patients and clinicians (acceptability -- "this tool is something I would want to use"; appropriateness -- "this tool would fit well in visits like today's"; feasibility – "this tool would be feasible to use in visits like today") in a close-ended fashion. Debriefing interviews will also include opportunity to review video of key moments from prototype tool use in those patient-clinician conversations.

Step 3. Later Prototyping. **A revised prototype will incorporate user concerns from early prototyping.** Promising, revised prototypes from the earlier phase that were rated acceptable will be subsequently tested in a later prototyping/user-testing phase. In this phase, the mature CG will be used with 15 unique new patients at various points on the perioperative care continuum. Qualitative field notes from observation and debriefing interviews will assess *acceptability and appropriateness*. As part of this process we will engage users in determining the most promising points in the perioperative care trajectory.

Sub-aim 1a analysis. **Our analysis for this sub-aim borrows constructs from implementation research and user-centered design.** Rapid prototyping in Steps 2 and 3 above are a rigorous and reproducible inductive, iterative methodology used in design activities. Its inferential frame blends quantitative ratings about *acceptability* (patients) and *appropriateness* (clinicians) with inductive qualitative content analysis, combining elements of participant observation and in-depth interviewing. A prototype with a median acceptability rating lower than 9 on a 10 point scale after step 3 with be further revised and run through similar iterations until it garners a median acceptability rating of at least 9/10.

Deliverables. The result of the Aim 1a activities will be a fully functional CG that conforms to international standards for decision support tool design and that will provide two key output elements for perioperative care: 1) a visible summary of the patient's pain priorities, balancing *pain control*, *side effects, mobility*, *alertness*, *cost*, *benefit to other symptoms*, and 2) a prioritized list of NPPC modalities that are available and interest them. These two key elements will comprise a new tab in the Epic Synopsis views entitled "my preference menu" that will be revisable, visible, and mandatory for all elective surgeries once a cluster is randomized. Contents of this report will also be printable for patients who prefer a hard copy. We have secured agreement from our practice leadership, that this CG and the resulting output become mandatory elements and will be maintained after the study if effectiveness is demonstrated (please see letter of support).

C.7.iii. Subaim 1b. In this aim we will configure Epic EHR CDS tools and interfaces relevant to each perioperative touchpoint (**Figure 5**), and conduct rigorous usability testing. A shared Epic EHR unites the MC HCS and offers high implementation fidelity across the HCSs that otherwise differ in geography, demographics, and other characteristics. Dr. Cheville (co-PI) works extensively with the MC EHR Oversight Committee (EROC), and helped to develop the processes by which EROC reviews, approves and resources EHR research studies. The NOHARM CDS tools have been robustly shown to enhance the alignment of clinical care with guideline recommendations across diverse populations, settings, and clinical targets.[147-149] The tools were selected for ease of specification, availability in the Epic foundation system, relevance to NPPC adoption and opioid de-adoption, and evidentiary support.[150] Our team has built, usability tested, and implemented iterations of the proposed NOHARM Epic CDS for our current NCI-funded pragmatic trial (UM1 CA233033).

Perioperative Care Pathway

1. **Access conversation guide via portal:** Develop individualized NPPC plan

2. **Presurgical check in:** Confirm NPPC plan, revise per preference, view video PRN

3. **In-hospital therapy:** Initiate NPPC plan, emphasize self-management, adapt PRN

4. **Hospital discharge:** Review NPPC plan, provide supplies, education, & local resources

5. **Access conversation guide via portal:** Refer to NPPC resources, complete PRO screening

6. **Post-operative clinic follow up:** Query use of NPPC, trouble shoot, opioid taper PRN

Potential adverse event - increased pain: Alert clinical team, prompt referral

Potential response: Medication Therapy Management visit with pharmacist

During the UG3 phase, we will develop CDS specifications in the Epic Proof of Concept (POC) environment, refine this build through focus groups and formal usability testing, and advance the build to the Epic Production (Prod) environment for pilot testing in the HCSs. We will use rapid cycle testing to pilot test changes to the build. Quantitative usability metrics will include effectiveness, efficiency and satisfaction.[151-153] Effectiveness is defined as the % tasks completed. We will track the number of mistakes, omissions, or deviations from recommended sequence that a participant makes in interacting with the CDS. Efficiency is defined as minutes for successful task completion. We will assess clinicians' satisfaction with the CDS using the validated System Usability Scale,[154] and components using the Single Ease Question, "Overall, this task was…Very Difficult (1) to Very Easy (7)."[155] We outline the build functionalities that we will develop during the UG3 phase below.

Figure 5.

Touchpoint 1 – Remote CG use. This build will establish discrete Epic data elements for NPPC preference data captured in the CG grid. These data will be stored in the Epic Questionnaire Masterfile and drive CDS.

Touchpoint 2 – Preoperative intake. Integral to day-of-surgery intake workflows, nurses will confirm patients' NPPC preferences, and query if they wish to update their preferences. Patients who have not will be offered the opportunity access the CG on a tablet. This build will involve flowsheet modification.

Touchpoint 3 – Acute hospital care. Post-operative PT and nursing orders will include instructions to administer preference-concordant NPPC modalities, or, for self-initiated practices, to prompt patients and ensure the availability of needed supplies, instruction, and ambient conditions, e.g., privacy. Additionally, nurses will be prompted to suggest alternative NPPC modalities if patients are not experiencing adequate pain relief. During patients' acute hospital stay, in order to raise awareness of opioid harms, and enhance clinician support for patients' NPPC use. This build will specify: 1) logic to auto-populate clinicians' notes with patient-specific opioid consumption and NPPC use data; 2) development of a designated opioid/NPPC graphic summary, "Synopsis" view for rapid, intuitive assessment of patients' pain and opioid/NPPC usage patterns; 3) preconfigured NPPC orders as "SmartSets" (**Figure 6**); and 4) pain flowsheet modification to include patients' preferred NPPCs with nurse directed prompts to initiate and support them.

Touchpoint 4 – Hospital discharge. Discharge summaries will be auto-populated with patient-specific opioid tapers, NPPC instruction and local NPPC resources. During the discharge process, nurses will document review of opioid harms and tapering, and NPPC preferences. Discharge planning will facilitate continuation of patients' NPPC use at their post-acute care locations by transmitting PT and nursing orders to rehabilitation facilities and home care organizations. Patients will be given prescriptions to receive local NPPC, if available. This build will auto-populate discharge summaries and orders with individualized opioid and NPPC content.

Touchpoint 5 – Remote CG use.   Irrespective of discharge location, patients will be prompted via the portal to interface with the CG for weekly PROMIS pain intensity, anxiety, and function reporting, and updating of NPPC use and preferences. This build will specify logic to ensure appropriate timing of portal prompts. Triggered functionality (below) will be available if criteria are met.

Touchpoint 6 – Postoperative outpatient follow-up.
During in-clinic postoperative checks, the CDS listed for Touchpoint 3 (Synopsis, SmartSets, and note auto-population) will be operational to alert clinicians of persistent pain and promote use of NPPC. Triggered functionality (below) will be available if criteria are met.
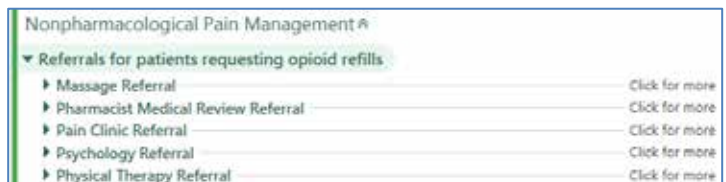

Nonpharmacological Pain Management ⌃

▾ Referrals for patients requesting opioid refills

▸ Massage Referral ———————————————— Click for more
▸ Pharmacist Medical Review Referral ———————— Click for more
▸ Pain Clinic Referral ————————————————— Click for more
▸ Psychology Referral ———————————————— Click for more
▸ Physical Therapy Referral ——————————————— Click for more

Figure 6.

Triggered Touchpoints – Opioid refill requests during the 3-month postoperative interval will trigger EHR CDS functionality including: 1) portal-based screening for misuse; 2) care team inbox messaging; and 3) best

practice alerts (BPAs) (**Figure 7**), that are soft stop for first refill request and hard stop thereafter. The alerts will include links to referral orders to pharmacists for medication review, PT, pain clinic, and psychology, as well as links to patient-specific UPOU and pain information. Threshold PROMIS pain, anxiety, and function scores will trigger cascading questions to solicit patients' preferred clinical response, e.g., call from team, PT referral. Scores reflecting severe symptoms or disablement will trigger EHR inbox team messaging. Collaborative care approaches to manage pain, anxiety and functional decline that have been validated in Drs. Cheville's and Kroenke's (consultant) previous clinical trials will be made available to surgical care teams.[120-123]

C.7.iv. Subaim 1c. In months 6 through 12 of the UG3 year we will pilot test all aspects of the protocol for the intervention in one surgical practice in each of our four HCS. The pilot clinic in each HCS will be chosen based on how reflective the clinic is of the HCS and remaining clinics (i.e., not randomly). The 4 practices will be selected no later than month 6, and in months 6-7 we will roll out the bundled CG and CDS interventions. The interventions will be implemented in months 8-9. During months 9-10 we will extract, merge, and clean data. In month 11 we will conduct measurement validation activities and preliminary analyses. Exit interviews with 5-10 key clinicians will occur in month 11.

Figure 7.

Facility implementation. Four surgical practices (one from each site) will be selected by month 6. Dr. Cheville and the site-PIs from each HCS will then arrange a telephone meeting with the senior administrators of each facility and schedule an in-person training of all clinicians in the clinic.

Intervention preparation. Our team will travel to the four HCS to apprise site leads of study implementation (We will also offer training webinars and on-line access to the training and NOHR

Intervention implementation. The intervention is intended to be practice specific during months 8-9 for surgical care of the selected condition and specialty (e.g. colorectal surgery).

Data management. In months 2-6, a pilot study database will be created with all the fields needed for the preliminary analyses. In months 6-12, we will pilot the extraction of EHR data needed to identify and describe the population and to ascertain OMEs and PROs.

Patient-centered outcomes. During months 10-11 study coordinators will implement debriefing interviews and structure data extraction for 15 patient at each site to insure feasibility of approach.

Preliminary analyses. Variables will be constructed from the EHR. Preliminary analyses will be limited to descriptive statistics outcome measurement in those target cohorts. We will replicate the outcomes as closely as possible within the limited time frame.

Measurement validation. After identifying patients from Epic registries and assessing their outcomes using the EHR dataset, our site PIs will obtain de-identified actual medical record information about these individuals to validate their diagnoses and outcomes using established manual chart review methods.

C.8. Specific Aim 2. To test the impact of a bundled NOHARM conversation guide + clinical decision support intervention embedded within an EHR on postoperative opioid use, pain, and function.

C.8.i. Overview. Aim 2 will characterize the effect of the NOHARM bundle on clinical outcomes, associations between stakeholders' use of bundle components and clinical outcomes, and the heterogeneity of its effect across key subgroups distinguished by preoperative opioid use, sex, age, and procedure.

C.8.ii. Cluster-randomized stepped wedge design. The cluster randomized stepped-wedge design will allow us to stagger the NOHARM implementation while increasing statistical power.[156-158] By allowing each site to serve as its own control, it reduces the bias due to imbalanced risk factors across clusters. Contamination does pose some threat to the internal validity of stepped wedge designs when, as here, the intervention rolls out sequentially in adjacent clusters. The 18 NOHARM clusters will minimize potential contamination by capitalizing on geographical separations in the built environments used to deliver perioperative care including different buildings in some cases, as well as subspecialty-designated inpatient wards, office suites, etc.   MCR, MCA, and MCF will each contribute 4 clusters distinguished by surgery type. Contamination is of limited concern in the MCHS as facilities are separated by $\geq$25 miles. Clinician cross-coverage is considered in the 6 clusters: Lake City & Redwing, MN; Fairmont and Mankato, MN; Barron & Rice Lake, WI; Albert Lea & Austin MN, and Decorah, IA; Eau Claire & Menomonie, WI; La Crosse & Onalaska, WI.

Allocation. There will be 5 "steps" in our design, 6 months apart. Each step is preceded by a baseline "Pre-NOHARM" period that will provide data for a within-site control group for each site. Every 6 months, beginning in year 2, 3-4 clusters will be randomly selected to receive the NOHARM intervention. The allocation is

illustrated in **Figure 3**. To ensure balanced cluster characteristics we will stratify steps on size and site.

C.8.iii. EHR logic operationalizes random allocation of the NOHARM bundle. When a cluster initiates the NOHARM intervention, its "activated" status will be operationalized using EHR logic capabilities. Specifically, clinician-based Boolean "CER" rules will be updated to include the ID numbers of cluster surgeons. Thereafter, patients will be placed on an Epic registry when they schedule a qualifying surgery with an "activated" surgeon. Registry membership is a characteristic that Epic CER rules evaluate as true (on registry) or false (not on registry). CER rules can thus trigger portal messaging to introduce the CG, and cause bundle components to appear on the EHR interfaces of clinicians who subsequently interact with the patient. When a surgeon's ID number is "activated," additional CER rules will ensure that NOHARM CDS becomes active on their interface.

C.8.iv. NOHARM intervention. The NOHARM bundle is designed to steadily apply "brakes" to postoperative opioid consumption, and "gas" to the uptake of NPPC approaches selected for their diversity and robust evidentiary support, **Table 1**. The bundle relies on brief, successive, but highly consistent multi-stakeholder EHR- and portal-delivered prompts and messaging. Because broad, pragmatic scaling and implementation are vital for public health impact, and because human resource deficits have proven a barrier to NPPC access,[159] the bundle leverages the EHR to coordinate, deliver, and individually "dose" NPPC.

Manage patient expectations regarding pain, opioids, and NPPC. The CG provides preoperative education that: 1) advises patients to anticipate postoperative pain, 2) emphasizes the importance of pain control, 3) explains appropriate opioid use (addressing pain at the operative site to increase activity, but not treating non-pain symptoms or chronic pain with opioids), and 4) clarifies opioid harms and causes of UPOU. Education principally occurs via the CG at touchpoint 1 (**Figure 5**) but will be reinforced by clinicians at points 2, 3, 4, and 6. Reports suggest that perioperative pain and opioid education is effective in reducing opioid use up to 50% prior to C-section, THA/TKA, and other elective surgeries.[17,160]

Normalize, promote, and deliver NPPC. The CG guides patients in identifying preference-aligned NPPC in four classes; exercise, physical modalities, mind-body, and touch. Touchpoints 2-5 normalize NPPC use by: 1) requiring NPPC preference documentation on hospital intake and discharge forms, and 2) presenting clinicians with patient-specific NPPC information. Touchpoints 1, 3, and 5 integrate NPPC into perioperative care by providing preference-matched PT and CHA referrals, HCS and regional NPPC resource lists, bedside NPPC education (DVDs that can be played on in-room TVs), and preferred pain-directed exercise and physical modalities in patients' acute and post-acute rehabilitation. Distal (5 and 6) and triggered touchpoints will ask about NPPC use and prompt patients to revisit the NPPC CG, particularly in the event of opioid refill requests or poorly controlled pain. Reports suggest that repeated prompts and navigational support are moderately effective in promoting use of rehabilitative and CHA approaches.[161-163]

Identify and appropriately support patients at risk of UPOU and/or poor surgical outcomes. The NOHARM bundle CG will direct patients at risk for UPOU due to preoperative opioid use, chronic pain, substance abuse, or mood disorders to HCS-based resources.[164] EHR interfaces and CDS will raise clinicians' awareness of UPOU risk by including patients' risk factors in auto-populated clinical notes, a Synopsis view, and alerts. Additionally, the EHR will present orders matched to risk-specific needs, e.g., pain clinic or psychology referral. Patients may develop UPOU risk from intense postoperative pain or anxiety. These domains are captured in inpatient documentation and will be tracked after hospital discharge. For moderate ratings, patients will be prompted to request needs-matched referrals and directed to NPPC resources. For severe ratings, Inbox messaging will be sent to the surgical care team. Reports indicate the identifying and preemptively intervening among patients at risk for chronic pain and pain-related disability is moderately effective.[165,166]

Apply behavioral economics principals to discourage opioid refills. Opioid refill requests will trigger portal-based administration of validated items from the Current Opioid Misuse Measure (COMM) (**Appendix A**).[167] The first refill request will trigger a soft stop BPA that will: 1) present COMM responses; 2) list NPPC preferences; 2) link to SmartSet referrals (NPPC provider, PT, pharmacist, etc.); 3) link to the Synopsis view; and 4) offer the option to send patients a dose-matched opioid taper. For subsequent refill requests, the BPA will be hard stop, i.e., a clinician must select a course of action before proceeding. Clinicians' responses to BPAs will be tracked through established Epic functionality.

Strong evidence supports "hard stop" alerts, as a recent review noted that 79% improved health outcomes and 88% process outcomes.[150] CDS that operationalize behavioral economics principles are gaining traction and show promising effectiveness.[168] Postoperative opioid refills are an important target as a recent report noted that each refill was associated

opioid use increased the risk of misuse by 20%.[169]

C.8.v. Primary and secondary outcomes, process measures

	Mode	Pre op	In hosp.	Dis charge	Rehab Facil.	Outpt. clinic	0-3 mo.	3 mo.
Opioid use								
OMEs	Self-report	✓*				✓	✓	✓*
OMEs	RN logged		✓		✓			
Prescriptions	EHR	✓		✓	✓	✓	✓	
Refill requests	EHR				✓	✓	✓	
Pain								
PROMIS CAT	Self-report	✓*				✓	✓	✓*
NRS	RN logged		✓		✓			
Function								
PROMIS CAT	Self-report	✓*				✓	✓	✓*
6 clicks	PT logged		✓					
Anxiety								
PROMIS CAT	Self-report	✓*				✓	✓	✓*
NPPC use								
Modalities	Self-report	✓*				✓	✓	✓*

Table 3. NOHARM outcome collection schedule.
* Inclusion in surgical outcomes monitoring program

Opioid use. We will abstract opioid prescription refill requests and prescribed dosages from the EHR. Patient-reported opioid consumption will be collected via the portal 3 months after surgery and at all touchpoints following hospital discharge using a validated questionnaire (**Appendix A**).[170] Response rates for portal-based reporting are $\geq$80%. As in previous work,[39,98,170] opioids prescribed or consumed will be converted to a singular measure of OME based on established conversion methodology, providing one metric of opioid use. NOHARM trial outcomes are listed in **Table 3**.

PRO measures. Pain intensity, anxiety, and physical function will be assessed with PROMIS CATs among patients pre-operatively and at 3 months following surgery. In addition to strong endorsement by the NIH,[171,172] IRT-based instruments have generally better discrimination across the entire trait range than legacy PROs,[173,174] and CAT administration enhances measurement efficiency and precision.[175,176] The PROMIS item banks have been validated in the target populations.[177-179] Hospital-based PRO collection will include the validated pain intensity numerical rating scales (NRS) and the 6 clicks functional assessment.[180,181]

NPPC use. Patients' use of NPPC will be captured via the portal on a CG-linked interface with a checklist.

Health care utilization. Healthcare utilization for NOHARM will consider hospitalizations, post-acute care, ED visits, surgery clinic outpatient visits, and calls to the surgery care team and post-acute care (PAC). EHR entries and administrative billing data will be aggregated to construct a comprehensive data set of all clinical encounters. Data collected for hospitalizations will include procedures and admission and discharge diagnoses. For ED encounters, we will capture diagnoses and procedures. Clinic visits will be captured using billing data which will include CPT codes, ICD-10 codes, location, and clinician NPI numbers. A recent audit established that 87% of calls to surgery clinicians were recorded in the EHR.

Process measures. Process measures reflecting patients' and clinicians' use of the NOHARM bundle components will be assessed through Epic's highly developed CDS usage capture capabilities. Process measures for patients will include frequency of: 1) accessing the CG, 2) viewing the video, 3) messaging for opioid/NPPC information/support, 4) updating preferences in the CG, and 5) requesting prescriptions/referrals.

Process measures for clinicians fall into three categories: 1) Use of cross-cutting CDS: a. retention of auto-generated text, b. frequency of accessing Synopsis, and c. frequency of issuing preconfigured Smartsets; 2) Touchpoint 2-4 completion rates for therapist- and nurse-entered NPPC and opioid documentation; 3) use of triggered CDS including frequency of: a. responding to BPA alerts, b. linking from the BPA to the Synopsis view and SmartSets, and c. NPPC referrals in response to opioid refill alerts, PRO scores, and Inbox requests.

C.8.vi. Specific Aim 1 Analyses. We will summarize patient characteristics (sex, age, insurance status) by intervention status (pre- versus post-NOHARM implementation). All patients will be analyzed on an intention to treat basis; this principle will be extended to the cluster status, so that delays in implementation of an intervention will not affect the intervention status of patients.[158] All methods will account for correlation of outcomes within clusters and across patients, and be appropriate for exploiting the stepped-wedge design. To test the primary hypotheses we will use generalized models to assess the effects of the interventions.[158] Our main model will be a mixed effects (i.e., multilevel) generalized linear model specified as follows. Let Y_{jkt} be the jth patient's OME at month 3 after surgery in the kth cluster (k =1,…,18), during step time period t (t =1,…,T).. The OMEs model is then,[158,182]

$$Y_{jkt} = \beta_0 + BX_{jkt} + \beta_N N_{kt} +$$

outcomes we will perform pre-specified analyses on key subgroups of patients who we anticipate may respond differently to the intervention. These are patients with and without pre-operative opioid use (non-naïve vs naïve), patients over 65 and under 65, men and women, and patients with above average versus below average pain scores post surgery. For each subgroup contrast we will first estimate model (1) within each subgroup (e.g. men), then estimate a model using all patients in which (1) is modified to include an indicator for subgroup and an interaction with the exposure variable N_{kt}. These analyses will provide insight into whether the NOHARM is more or less effective within these subgroups.

<u>Analytic considerations</u> Data will be examined for patterns of missingness. Covariates missing at random (MAR) or missing almost at random (MAAR) will be included in analyses through multiple imputation. Loss to follow up will be compared across intervention periods to assess for attrition bias; if loss to follow up differs by intervention status, we will perform worst-case scenario sensitivity analyses under the assumption of a maximum effect ratio.[183]

<u>Statistical power:</u> Stepped wedge cluster randomization trials typically have more statistical power than other cluster randomized designs.[157] This is because each cluster is able to serve as its own control, accounting directly for the within cluster correlation of outcomes. In addition, the impact of intra-cluster correlation on power is typically smaller than on conventional cluster randomized trials.[182] For the current study, the number of clusters is fixed at 18, and the anticipated number of patients is 140,000 over the entire study period; thus, we estimate detectable effects based on these numbers, assuming a substantial loss to follow up of 20%. Using data from a prior study [ref],[98] we calculated the intra-procedure correlation for OMEs prescribed and consumed and found = 0.33 and 0.27, respectively. We used the upper estimate, = 0.33, to calculate the design effect DE_{SW} based on the formula:[157]

$$DE_{sw} = \frac{1 + \rho(ktn + bn - 1)}{1 + \rho\left(\frac{1}{2}ktn + bn - 1\right)} \cdot \frac{3(1-\rho)}{2t\left(k - \frac{1}{k}\right)}$$

where k = 6 is the number of steps (including baseline), b = 1 is the number of measurements per patient in the baseline step, t = 1 is the number of measurements per patient at each step, and n is the number of patients per cluster. Assuming 80% follow up and equal distribution across clusters, n = 140000*80%/18 ~ 6,222. Rounding to 6,000, we get DE_{SW} = 0.36, or an effective sample size of N_{eff} = 140,000x(80%)x0.36 = 20,100 patients. Thus, even with substantial intra-cluster correlation we will have 90% power to detect a true difference of 0.03 SDs between intervention groups with a maximum probability of a Type II error of = 0.05. Given this very small detectable effect, we anticipate that the challenge will not be detecting true differences but in assessing meaningful differences. For the subgroup analysis, the same type of calculation shows that we will be able to detect even small true effects of 0.2 SD in subgroups as small as 3% of the study population.

C.9. Specific Aim 3. To conduct a mixed-methods evaluation to understand and reduce disparities in the adoption and implementation of the NOHARM bundle components among patients at risk for UPOU.

C.9.i. Aim 3 Overview Aim 3 will apply rigorous mixed methods to characterize the uptake and effects of the NOHARM bundle among patients at high risk of UPOU; those with psychiatric disorders, active or prior substance abuse (including nicotine and alcohol), and preoperative opioid use.[23,26,184-187] Reports indicate that >60% of converters have ≥1 of these characteristics.[22] Aim 3 will identify factors that facilitate and impede NOHARM bundle use to inform future iterations.

As highlighted in our conceptual model, disparities in UPOU rates likely stem from healthcare system, clinic, provider and patient factors.[188] The NOHARM bundle's collective targeting of these factors affords a unique opportunity to assess

Dimension	Outcome	Disparity focus
Reach (proportion) of those eligible that use the NOHARM toolbox	Toolbox usage rates of among UPOU high risk	Differences by UPOU risk factors, race/ethnicity, and SES
	Reasons for use/non-use	Comparative analysis of reasons for use/non-use
Effectiveness (OMEs, changes in PROMIS CATs; reductions in healthcare utilization)	Change in PROMIS CATs and daily OMEs	Differences by UPOU risk factors, race/ethnicity, and SES
	Resasons for change or lack of change in PROMIS scores and OMEs	Comparative analysis among responders of experiences with CE and toolbox
Implementation (as intended in the real world)	Challenges for fidelity to intervention/ implementation	Challenges for implementation for high-risk groups
Maintenance (extent to which a program is sustained over time)	Maintenance of % of patients sent ePROS and responding	Maintenance/improvement of toolbox usage, changes in PROMIS scores and OMEs in high risk groups.

Table 4. RE-AIM Framework Adapted form Glasgow et al.

disparities in the intervention's adoption and implementation that can inform tailoring for high-risk groups.[188] After quantitatively evaluating differences in CG usage across subgroups, we will conduct qualitative interviews with high and low CG users with purposive sampling of patients who may have lower IT familiarity, to understand barriers and facilitators for use among the three clinically-defined, electronically ascertainable high-risk groups. Second, we will quantitatively evaluate the intervention's effectiveness among these groups, and then qualitatively compare experiences among those who do and do not engage in UPOU at 3 months after surgery. We will solicit suggestions on how to refine the intervention to improve uptake of NPPC.

C.9.ii. Aim 3 Conceptual Model. Our evaluation will be guided by the Reach, Effectiveness, Adoption, Implementation and Maintenance *(RE-AIM) framework*.[189,190] RE-AIM provides a framework for identifying the quantitative and qualitative approaches best suited for these dual effectiveness and implementation aims, as shown in **Table 4**. We concentrate on those components of the framework that evaluate if the intervention: 1)

is accessed/adopted (Reach); 2) reduces disparities in pain control and UPOU (Effectiveness); and 3) is implemented consistently (Implementation and Maintenance) across high risk subgroups.

C.9.iii. Mixed Methods. We will follow a mixed methods sequential explanatory design to evaluate patient variation in the implementation of the intervention. We will use EHR data, as described in Aim 2 (§C.8.v-vi.), to assess quantitative usage and outcome data, and follow analysis of the quantitative data with qualitative inquiries to help explain and elaborate on the quantitative findings. This approach will afford insight regarding how the NOHARM toolbox may differentially affect high-risk subgroups and implementation improvements.

Study Population. Generalizing from patients who underwent qualifying surgeries within MC HCS in 2018, 27% of the study population will use opioids preoperatively, 37% will have been assigned an ICD-10 code for a mood disorder in the 12 months prior to surgery, and 29% will have abused alcohol, nicotine, or drugs within this time frame. For qualitative interviews, we will purposively select 17 participants equally from the three high risk groups. To capture a broad set of experiences, we will balance within our interview strata patients from different HCS undergoing different surgeries. *Patients who participate in the interviews will provide consent*.

Qualitative Methods. We will use a stratified purposeful sample of patients for interviews. Starting with the 3-4 clusters first randomized to the NOHARM intervention, as outlined in **Figure 3**, we will identify patients at high risk for UPOU. We will then identify high CE users and low users and recruit from both groups for interviews. Interviews will occur shortly before or after hospital discharge. Our second set of interviews will be conducted 3 months after surgery and will be aimed at understanding barriers and facilitators to effectiveness of the NOHARM bundle in reducing UPOU and improving PROMIS scores. Our intention is to interview the same patients as they move across the perioperative trajectory, but to fill in when there is attrition or when more informants are needed to fill a category; e.g., if few patients with mood disorders develop UPOU, we will recruit additional patients who continue using opioids. A semi-structured interview guide will be developed using domains consistent with the RE-AIM framework, as well as topics relevant to preliminary analysis of the quantitative data. The guide will be structured to ensure sufficient uniformity across interviews, and to allow comparisons by strata, but allow patients to frame issues according to their own experiences and words.

Data Collection and Analysis. We will conduct 30-45 minute interviews by phone. They will be audio recorded with permission and transcribed for analysis. The interview schedule will follow an iterative process of data collection and analysis to ensure the identification and testing of analytic categories until thematic saturation has been achieved. Qualitative analysis of interview transcripts and field notes will use a theoretically driven thematic approach.[191] The study team will begin by reading the textual data, discussing manifest and latent content, and developing a list of concepts represented in the data. These concepts will be reviewed in light of relevant implementation constructs, but not be constrained by them. A coding framework will be developed using these concepts and applied to the text data. Coded data will be entered into NVivo 11.4 (QSR International Pty Ltd.) to facilitate data organization and maintain an audit trail of the analysis. Members of the study team (JT, AL) will meet to discuss the data and narrative memos will be used to describe themes or major findings in the data, along with variation in experience. Implementation metrics, and individual- or site-level characteristics of interview participants will be used to aid in interpretation. A side-by-side comparison of qualitative and quantitative findings,[192,193] will further explore how findings converge or diverge in order to enrich understanding of disparities in NOHARM uptake. Data and methods triangulation, along with the inclusion of study team members from different disciplines, will enhance trustworthiness of inferences.[194] The coding framework will be applied to generate a matrix of results,[195,196] allowing for within- and across-case analysis. This approach will facilitate systematic but flexible analysis of variation by UPOU risk factors.

Application of findings. The qualitative interviews will include questions about ways to overcome barriers and to enhance facilitators to increase NPPC use. As part of our RE-AIM evaluation, we may identify straight-forward refinements based on the mixed methods that could reduce disparities. Therefore, we will meet with our Study Consultants, NOHARM team, and NIH PRISM representatives to prioritize solutions. Then, through a collaborative decision process, determine if a solution should be: 1) immediately integrated into the NOHARM intervention, 2) considered for future iterations, or 3) not recommended.

C.10. Limitations, Alternative Strategies, and Contingencies. We have anticipated several potential limitations, and considered alternative strategies and planned for a range of contingencies. 1. Patient engagement to consistently use the CG. We will use proven effective strategies to increase CG use: 1) having schedulers emphasize CG importance and assist with portal registration; 2) sending auto-reminders to CG non-users from their surgeons; and 3) providing the CG via tablet during surgery check in. Patients who do not use the CG preoperatively, as may occur with C-sections, will be able access it post-operatively in the hospital. 2. Clinicians will ignore the CDS. User-centered design and UG3 rapid-cycle usability testing will emphasize CDS value and efficiency. Some CDS tools are non-ignorable, requiring input before a workflow can continue. Pilot process measures will identify lesser used CDS and provide an opportunity to address remediable issues. 3. Fidelity. Tightly controlled implementation of the intervention by research staff will not be possible

consequent to our pragmatic design. However, our systematic collection of extensive process data will provide insight into variations in intervention uptake and fidelity that can be assessed with sensitivity analyses. 4. Coordination across 4 HCSs. Our team has successfully implemented interdisciplinary perioperative initiatives and conducted multi-site clinical trials (R01CA163803 & UM1CA233033) involving the 4 HCSs. We will leverage successful cross-HCS engagement and coordination approaches used in these trials, and Dr. Abdel's (co-I) initiative to promote use of regional anesthesia for orthopedic surgeries.

1.   Risk to Human Subjects

a.   <u>**Human Subjects Involvement, Characteristics, and Design**</u>

Patients with undergoing qualifying surgical procedures who receive care at a Mayo Clinic Health System will be exposed to the ***<u>N</u>on-pharmacological <u>O</u>ptions in postoperative <u>H</u>ospital-based <u>A</u>nd <u>R</u>ehabilitation pain <u>M</u>anagement (NOHARM)*** intervention. The assessments conducted in this study will consist of self-administered questionnaires that are integral to routine perioperative PRO assessments and are established components of standard MC care, as well as semi-standardized qualitative interviews. The NOHARM intervention strives to offer safe and effective non-pharmacological pain care (NPPC) options that are matched to patients' preferences. Patients will not be required to accept any NPPC and they will be assured that their surgical care will not be impacted by their decision whether to interact with the NOHARM conversation guide (CG) or to utilize suggested NPPC.

The evaluation instruments for the NOHARM trial are validated clinical tools to measure pain, anxiety, and physical function. For the NOHARM trial, PROs will be administered both via synchronous and asynchronous electronic modes. We estimate that 140K patients will participate in this pragmatic trial. During the pre-NOHARM phase of the trial, there will be no intervention-related effects on patients' care. Once the NOHARM intervention is initiated, patients will be: 1) encouraged to interact with the CG via their patient portal to develop a personalized NPPC plan; 2) reminded of their NPPC plan during day-of-surgery intake processes; 3) provided opportunities from nursing and physical therapy to receive NPPC during their hospitalization, 4) asked to revise their NPPC plan, as needed, on hospital discharge and provided with support and resources; 5) encouraged to use the CG during their rehabilitation to revise their NPPC plan as needed; 6) queried about their NPPC during their postoperative clinic follow-up appointment; and, if they request a second opioid refill, 7) required to complete PROs screening for mood disorders, opioid misuse, and functional decline.

Regarding age, all patients 18 years and older are eligible. Since the intervention is essentially an enhancement of standard perioperative care to better align pain management with guideline recommendations. all patients undergoing qualifying surgeries will be eligible. Patients who are unable to interact with the portal-based CG will not provide the data needed to populate and drive the EHR-based algorithms and clinical decision support tools. Therefore these individuals will be more limitedly exposed to the intervention. They will be encouraged to use the CG during day-of-surgery intake processes, but this may not occur due to many competing demands. Inability to complete the ePROs may be related to cognitive limitations, lack of English fluency, or psychiatric illness.

This trial does not involve special vulnerable populations, such as fetuses, neonates, children less than 18 years old, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. However, pregnant women who are scheduled for C-section will be encouraged to interact with the CG to develop an NPPC plan.

Patients will provided NPPC treatment recommendations based on the current evidence base and guidelines, both of which will be reviewed annually during the trial to assure continued concordance of suggested treatments with current recommendations. Treatments may span the behavioral and rehabilitative domains depending on the nature, intensity, and treatment responsiveness of a patient's pain, as well as their individual preferences.

b.   <u>**Sources of Materials**</u>

The research material that will be obtained from study participants will be restricted to data excerpted from their EHRs and data that they provide during qualitative interviews. All study outcomes, excepting the interviews conducted with patients for the Aim 3 qualitative research activities, will be electronically abstracted from the unified Epic EHR or the MC Unified Data Platform. *Data collected from patients who have not given permission for use of their EHR data for research will not be utilized in the NOHARM trial analyses, reported on, or transferred to the PRISM Centers or outside institutions.* Qualitative interviews conducted with study participants will solely occur with their approval as documented in written informed consent and HIPPA authorization. There are <u>no</u> biological or other specimens obtained as part of this research study.

The data gathered will be obtained directly from the EHR, excepting vital status, or during qualitative interviews and focus on the severity of symptoms (pain and anxiety), physical function, symptom-related NPPC treatments, OMEs, health care use, and sociodemographic information.

Only NOHARM study team members (study investigators, project coordinator, research assistants, nurses, data managers, biostatisticians) who are IRB-approved will have access to individually identifiable private information. Measures to assure privacy and confidentiality are described in Section 2.c.ii. below. Data that are transferred outside of the MC firewall will be de-identified, stripped of personal health information, and encrypted.

c. **Potential Risks**

Potential risks primarily involve direct adverse effects of FDA-approved NPPC modalities which have much more benign toxicity profile than opioids, and are robustly guideline-endorsed. NPPC adverse events are exceedingly rare. NPPC side effects typically resolve shortly after stopping them. Since some patients will have anxiety, another potential risk is emotional distress related to the discussion of psychological symptoms which is typically a minor issue and well handled by nurse and physical therapists. Suicide is an exceptionally rare event in medical patients enrolled in trials and safeguards are discussed below (section 2.c.i.).

The overarching goal of the NOHARM intervention is to ensure that validated and guideline endorsed NPPC is offered to patients. Patients will have the option to decline treatments or to discontinue them at any time. Their autonomy with respect to pain management will be repeatedly emphasized via different modes, e.g. introductory video, self-management educational sheets, clinical discussions, throughout the NOHARM intervention. Since pain under-treatment and non-beneficial opioid use are prevalent across the perioperative trajectory, and increase patients' risk of disablement, opioid use disorder (OUD), unplanned hospitalization and ED visits, and medical morbidity, the risk of non-exposure to effective NPPC treatments is more likely to deleteriously impact patients than their systematic exposure to optional, guideline-concordant treatments – the goal of the NOHARM intervention.

Alternative treatments for potential study participants include receiving perioperative pain control from their primary care physician or another specialist, receiving no treatment, or receiving treatments available through alternative community-based practitioners. The risks (failure of pain to improve, OUD) and benefits (symptomatic improvement) of these alternative treatments will be explained in the video that will be presented to all patients as part of the CG. As described below, the textual contents of the video will be available to all patients on request.

2. **Adequacy of Protection Against Risks**

a) **Recruitment and Transparency**

This is a population based study, where all eligible patients undergoing qualifying surgeries at MCR, MCA, MCF, and MCHS facilities will be enrolled. NOHARM will be sequentially implemented per the stepped wedge random allocation, and will consequently impact the roughly 40K patients treated by these practices annually. Neither current regulations, nor the peer-reviewed literature explicitly defines when a formal patient consent process is required for pragmatic clinical trials, particularly when testing the implementation of proven effective interventions at scale. This type of research, sometimes referred to as "standard of care" research in which the primary research objective is to implement and evaluate a strategy that better satisfies the existing clinical standard of care, has been debated in recent high profile cases.[70-72] Opinions from ethicists vary but all emphasize the vital importance of IRB engagement and assiduous efforts to foster disclosure and transparency across all relevant stakeholders.[73-75] We believe, and in consultation with our local Research Ethics Consult Service, have confirmed that this study meets the criteria for being standard of care research in which the marginal incremental risks of the proposed interventions do not foreseeably introduce even incremental net risk to individuals in the participating practices being studied. The MC IRB has been an active partner in developing the NOHARM application and its involvement will continue. IRB members and the MC Family Advisory Council contributed to the current NOHARM "*Transparency Promotion and Patient Preference Protection Plan.*"

The *Transparency Promotion and Patient Preference Protection Plan* is a multi-pronged approach that was in place prior to planning and design of the NOHARM trial, but that has further matured as a consequence of

these efforts. The MC Enterprise, in an effort to proactively anticipate ethics, human subjects protections, and institutional oversight concerns related to the conduct of quality improvement, pragmatic clinical, and "standard of care" trials convened a group of key stakeholders. These stakeholders include members of the MC IRB, MC Patient and Family Advisory Council, representatives from Enterprise Research Administration, and clinicians representing surgical specialties, pain management, pharmacy, rehabilitation medicine, and general internal medicine. This stakeholder group is entrusted to provide impartial oversight of trial activities that may challenge the goal of complete pan-stakeholder transparency and prioritization of patient preference.

In addition to adapting the MC *Transparency Promotion and Patient Preference Protection Plan* for the NOHARM trial, the stakeholder group described above, which is independent of the Data Safety and Monitoring Board, will meet quarterly during all years of the grant cycle to revise the plan as required and to address concerns broached by patients, caregivers, clinicians, or other MC personnel regarding the transparent and ethical conduct of the trial. The stakeholder group will additionally review all patient-directed NOHARM clinical materials with emphasis on clarity, literacy, and transparency. These activities will occur in parallel with IRB oversight of the trial protocol and its execution. The instructional video, described below, that will introduce patients and caregivers to the initiation of the NOHARM intervention, will be a key focus of stakeholder group oversight. Because the video is comprised of static slides with voice over, any suggested edits can be easily accommodated.

The NOHARM intervention patient-directed instructional video will be simply produced and will be available to patients as part of the CG via MyChart or during the day-of-surgery intake process. The video will be presented to patients at least once after the initiation of NOHARM intervention in an activated cluster. Additionally, a print version of the slides with narrative in text form will be available to patients on request. The video will present information about cancer-related symptoms, distress, and functional decline. It will describe pain under-treatment, the availability of effective treatments, and OUD. The NOHARM intervention will be described with emphasis on the points at which patients may decline care; e.g., acceptance of NPPC. The video will reassure patients that their surgical care will not be impacted by a decision to decline NPPC. The video will inform patients how to obtain more information about the NOHARM trial.

b) **Consent**

All clinicians and patients who participate in qualitative interviews for Aim 3 research activities will provide informed consent and HIPAA authorization. Briefly, a research assistant will conduct a telephone-based eligibility interview of eligible patients. For eligible patients, the study and interviews will be described in detail and written consent will be obtained from those who desire to participate. An informed consent packet (including HIPAA authorization) will be mailed to the subject, signed, and returned in a pre-addressed, postage paid envelope (with phone reminders if not returned).

c) **Protections Against Risk**

i) Patient Safety.

No experimental medications will be used in this trial. Rather, we will suggest NPPC modalities which are FDA-approved for treatment of pain and widely-used in clinical practice. Notably, the NOHARM intervention will only suggest NPPC and provide support and resources to patients who are interested in pursuing this option. Responses to NPPC as well as any side effects will be closely monitored. For patients who do not tolerate the side effects, the NPPC will be discontinued and alternative approaches suggested in their place. We will use careful evaluation of all subjects at baseline and close follow-up via in hospital observation and portal-based monitoring.

Women of child-bearing age (expected to be a minority of patients in our study sample, based the MC patients who underwent qualifying surgeries in 2017 and 2018) will be counseled about any potential adverse effects of NPPC modalities.

Some of the patients enrolled in this study will experience anxiety. The PROMIS item bank does not include a question about thoughts of self-harm. However, patients endorsing high levels of negative affect will be identified to their surgical teams with suggestions to screen for self harm. If such thoughts are detected by interview or spontaneously volunteered by the patient, we have an evidence-based algorithm that was developed in 3 earlier depression effectiveness trials in medical patients, and was tested in our two most

recent trials in general medical (SCAMP trial) and cancer (INCPAD trial) patients. By this algorithm patients are classified as minimal, lower, or higher risk. The latter constitute < 2% of patients enrolled in depression trials, and we have a protocol for expedited evaluation by a study physician for the rare patient in the higher risk group, also tested in the SCAMP and INCPAD trials. All research personnel will be trained by the PI in this protocol.

ii) <u>Participant Privacy and Confidentiality</u>

We will assure the privacy of the content of all interviews and other data collected as part of this study by assigning patients unique identifiers to track their individual data (rather than using names or hospital or social security numbers) following electronic abstraction from the Epic EHR and keep all records under lock with access only by study personnel.

Each of the study questionnaires has been programmed into the Epic EHR. Algorithms check for inappropriate or missed data entry, and prompt patients to enter complete data. Computer algorithms automatically score the questionnaires and store the summary scales in the Epic EHR. Once PRO data are abstracted from the EHR or MC Unified Data Platform, patient hospital numbers, names, addresses and other personal information will be restricted to authorized personnel to protect patient confidentiality. For data analysis and other uses of the data, this information will be removed from the database and be replaced with a simulated identification number. This strategy has been used in our previous clinical trials to efficiently screen and enroll patients, accurately complete follow-up assessment, and protect patient privacy. Our team has prior experience in setting up the protocols for data integrity and data back-up to minimize the risk for lost or inaccurate data.

Delivery of the intervention will include pain and anxiety monitoring via secure mechanisms and involvement of the study participant's surgical team. All exchanges of clinical information will comply with HIPAA standards of patient privacy, and all data collected, transferred, and stored for research purposes will be done in a manner to assure confidentiality.

3. Potential Benefits of the Proposed Research to Human Subjects and Others

Participants may experience improvement in their pain, anxiety, physical function and quality of life. Given the prevalence and burden of these symptoms in surgical patients, the benefits of developing and testing effective interventions are substantial.

Patients will not be charged for any of the NOHARM intervention components which will be integral to their surgical care. Patients will be financially responsible for all health care costs not directly associated with this study. They will be alerted to potential out-of-pocket costs associated with all NPPC modalities.

The risks to subjects are minor, and procedures or minimizing these risks are outlined in 2.c. The interventions tested are an evidence-based enhancement of standard care. The anticipated benefits of improved symptoms, physical function, and quality of life for study participants make the risk to benefit ratio reasonable in this trial.

4. Importance of the Knowledge to be Gained

Pain, affects large numbers of the majority of patients in the U.S. (and many more globally) who undergo surgery each year, and have potentially huge individual and societal costs in terms of quality of life, social and work functioning, health care use, OUD, opioid diversion and lost productivity. Knowledge regarding the effectiveness of the NOHARM intervention that will be tested in this trial and compared to standard surgical care (pre-NOHARM) has considerable potential for improving the health and quality of life of surgical patients. As noted, risks are low in this study and benefits are favorable. Therefore the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result from this trial.

Data Safety Monitoring Plan/Board

Core elements of the following multi-component Data Safety Monitoring Plan have been successfully used in our previous NIH-funded comparative effectiveness trials, including an NINDS-funded poststroke depression trial, an NIMH-funded SCAMP trial of pain/depression in primary care patients, and an NCI-funded INCPAD trial of pain/depression in cancer patients, **[*Additionally, this DSMP is compliant with our MC Scientific Review Committee DSMP guidelines.*]**

a) *Determination of Level of Risk.* *This study involves low to moderate risk: It is unlikely that serious adverse events will occur during the study.*

b) *Data and Safety Monitoring Board.*

We will establish a local Data Safety Monitoring Board (DSMB) that meets every 6 months during the study. Members will consist of non-study investigators and will include surgical specialists, a clinical trialist with expertise in effectiveness trials, a pain management physician, a nurse with expertise with care management, a clinical psychologist, an implementation scientist, and a biostatistician. This DSMB will review the adverse events and the collected data. A copy of the DSMB minutes and recommendations will be provided to the study PI and the IRB.

c) *Study Monitoring.*

i) *Frequent Study Participant Contacts by the surgical care team*. All participants are closely followed by automated symptom monitoring. NPPC responses as well as side effects are closely monitored. All interview responses are part of the study database.

ii) *Twice-a-Month Research Team Meetings*. In addition to the NOHARM Executive Committee meetings, the PI, Research Coordinator, research assistants, NOHARM allied health staff, relevant co-investigators, and other member of the Research Unit meet monthly for study operations meetings. These meetings will focus on monitoring adherence to study protocols, data collection, and adverse events. Minutes of these meetings will be maintained by the Research Coordinator. Reporting of any unusual events or problematic issues will be done by the study PI and/or Research Coordinator. Decisions will be made jointly and recorded in the minutes.

d) *Adverse Event Grading.*

- *The following scale will be used to assess the severity of the adverse event:*
    - *Mild - Awareness of sign or symptom, but easily tolerated*
    - *Moderate - Interference with normal daily activities*
    - *Severe - Inability to perform normal daily activities*
    - *Life Threatening - Immediate risk of death from the reaction as it occurred*
- *The following scale will be used to describe the relationship of the adverse event to the study intervention:*
    - *Definite: Adverse event clearly related to study intervention*
    - *Probable: Adverse event(s) likely related to study intervention*
    - *Possible: Adverse event(s) may be related to study intervention*
    - *Unlikely: Adverse event(s) doubtfully related to study intervention*
    - *Unrelated: Adverse event(s) clearly not related to study intervention*
- *The relationship of the adverse event to the therapy/study will be determined based upon clinical review of all data and subsequent clinical judgment.*

e) Explicit Definition of a Serious Adverse Event (SAE). *SAEs include the following:*

- *Death*
- *A life-threatening experience*
- *Inpatient hospitalization*
- *Prolongation of hospitalization*
- *Persistent or significant disability or incapacity*
- *Congenital anomaly*
- *Birth defect*
- *May require medical, surgical, behavioral, social or other intervention to prevent one of the above outcomes.*

f) *Adverse Event Reporting.*

- *All Serious Adverse Events that are unexpected and related to the study intervention will be reported to the IRB within 3 working days using their Prompt Reporting Form.*
- *All other adverse events will be reported annually with the continuing review.*

g) *Specific information evaluated at the time of each DSMB review.*

- *Recruitment, accrual and dropout statistics, number and description of any AE or SAE, any other additional concerns.*
- *Data collection – key issues*
- *A table with the number of adverse events and their severity will be used in the DSMB reports to assess the level of risk/toxicity that occurred.*

h) *Data Integrity and Security*

All documentation, once abstracted from the Epic EHR will be stored electronically on the limited-access MC Unified Data Platform or in locking file cabinets in a limited-access, locked project office. All electronic databases housing subject data will be password-protected, housed on a limited-access university server, with access limited to study personnel only. Identifying information is separated from all data provided by participants through the use of a unique identification code assigned by study personnel to each subject.

DATA MANAGEMENT AND RESOURCE SHARING PLAN

Data Privacy
Mayo Clinic upholds the most stringent standards for protection of human subjects and privacy while balancing the crucial importance of data sharing to advance medical science. This is applied to all patients participating in research activities, direct care and as study participants. Protection of privacy is assured based on Mayo Clinic's standards and procedures, including rules in full compliance with current HIPAA regulations. All staff members are trained in privacy compliance and held to the strictest standards. Mayo Clinic requires that formal approval be obtained from all appropriate committees before medical records are reviewed or patient contact is initiated.

Reporting Sensitive Information: Mayo Clinic has obtained a Certificate of Confidentiality from the Department of Health and Human Services (HSS). The Certificate is designed to prevent Mayo from being forced to disclose identifying information for use in any federal, state, or local civil, criminal, administrative, legislative, or other court proceeding, even if faced with a court subpoena. The Certificate does not prevent Mayo Clinic from taking steps, including reporting to authorities, to prevent serious harm to patients or others. The research team may share information with:
> HHS to complete federal responsibilities for audit or evaluation of research
> Public health agencies to complete public health reporting requirements
> Mayo Clinic representatives to complete responsibilities for oversight of a study
> Primary care physicians if a medical condition that needs urgent attention is discovered
> Appropriate authorities to the extent necessary to prevent serious harm to patients or others

Identifiers
In general, clinical data used for research is de-identified, whereby all information that could link to an individual patient's identity is removed. Patient information is coded and coding information secured. Individual participants are identified in computer files only by a unique study number, which bears no relationship to personal identifiers Healthcare information is utilized by staff solely on a "need to know" basis.

Confidentiality
Dissemination of healthcare and insurance information is entirely compliant with current healthcare information legislation. In the case of clinical information in research, all participants are required by Minnesota law to be informed of use of their information in research projects and have the right to decline participation. In addition, informed consent policies are rigorously employed and monitored. Every member of Mayo Staff, both clinical and research, must take training annually in patient information security to be fully compliant with Federal HIPAA regulations.

Disposition of Data
Along with the requirements of state privacy laws, and more recently HIPAA, strict institutional procedures have been put in place to help maintain patient (subject) privacy. All study records are kept in a password-protected electronic study folder. Individual participants are identified in associated computer files and analyzed only by a unique study number, which bears no relationship to personal identifiers. Only de-identified data will be entered into the electronic data record. Only the authorized personnel from the study team will have access to this data.

Sharing Study Results
Results of the study will be shared with participant subjects

Data Security
Mayo Clinic Rochester has a complete electronic medical record. With our long-standing commitment to privacy, extensive measures have been instituted to insure security of the clinical database. The mainframe computers and LAN are entirely behind an extensive information firewall that is routinely maintained and upgraded. Staff access electronic data only on a "need to know" basis. Staff access and use of this electronic medical record data is monitored by the Information Management and Technology Committee. Clinical Research Data is de-identified with respect to patient of origin and data management held to the same standards as clinical healthcare information. Hard copy data of patient information for research is maintained

in locked and secure cabinetry within the office of the study coordinator. Access to this building is carefully controlled by Mayo security and requires keycard access.

Managing data security is mandatory. Before accessing secured applications and data through the internet or intranet, each user will be required to login using their assigned user id and password. Group files will be maintained to control access to directories, applications, and data. The user ID must be a member of the group file in order to access the group's data or application. The groups are assigned roles to the data and applications (e.g., viewing authority to a protocol document, adding and updating patient data, etc.). To get to specific secured directories, applications, and data, the user ID and password are verified at a folder and application level; thus, members are restricted to viewing only applications and data that pertain to their role. Applications will also be run on secure socket layers.

Data Sharing
De-identified data collected for the NOHARM trial will be made available to the PRISM Centers and NIH after removal of participants' personal health information. The data will be encrypted per standard Mayo Clinic data sharing protocols. There is ample precedent for sharing de-identified clinical data collected in the course of care delivered by Mayo Clinic facilities. Specifically, the Mayo Clinic contributes extensive and diverse clinical data to OptumLabs (https://www.optumlabs.com/about/partners.html) for integration with administrative claims data. Additionally, the Mayo Clinic is a founding member of the High Value Healthcare Collaborative (https://www.highvaluehealthcare.org/). This collaborative aggregates complete clinical and administrative data from participating members' EHRs to address questions fundamental to increasing high value health care. A key agenda for both OptumLabs and the Value Healthcare Collaborative is the effective leveraging of "Big Data" to identify novel care delivery solutions.

We will adhere to the NIH Health Care Systems Research Collaboratory Data Sharing Policy:

1. Collaboratory investigators will each share, at a minimum, a final research data set upon which the accepted primary pragmatic trial publication is based.

2. The Collaboratory Steering Committee recognizes that sharing data derived from clinical care in studies performed in partnership with health care systems may, under some situations, require precautions in addition to those regarding patient confidentiality, to protect specific interests of collaborating health care systems, facilities or providers. Precautions such as allowing data sharing in more supervised or restricted settings, such as access to researchers who agree to limited pre-approved research goals, may be appropriate to address these needs in implementing this data sharing policy.

3. Consistent with NIH policy and guidance, Collaboratory investigators will choose the least restrictive method for sharing of research data that provides appropriate protection for participant privacy, health system privacy, and scientific integrity.

4. Collaboratory investigators will work with NIH to implement this data sharing policy, to ensure the appropriate administrative processes and technical infra-structure are in place to support timely data sharing for the Collaboratory

Sharing of NOHARM Bundle Components with Commercial Vendors
The NOHARM intervention requires an electronic platform for ePRO collection. With the industry-wide push towards patient-centricity, electronic clinical outcome assessments have become a more widely used strategy to streamline patient data collection, provide real-time access to data (for review and monitoring), and enhance patient engagement. These electronically collected data elements are comprised of a variety of captured assessments, including PROs, clinician-reported and health-care professional assessments, observer reported outcomes, and patient performance outcomes administered by health-care professionals. The main methods for collection of electronic data include computers, smartphones, and tablets, as well as telephone systems. The number of commercial entities offering such platforms has increased dramatically as the incorporation of electronic data collection platforms has become normalized in pharmaceutical trials. This normalization was spurred by the fifth authorization of the Prescription Drug User Fee Act (PDUFA V), which was enacted in 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA), and included a commitment by the FDA to more systematically obtain patient input on diseases and their treatments. In so doing, PDUFA

V supports the use of PRO endpoints to collect data directly from the patients who participate in clinical studies and to actively engage patients in their treatment. Additionally, as accrediting bodies are requiring monitoring of cancer survivors and the construction of individualized and updated survivorship care plans, e-platform vendors have expanded their product portfolios to include the functionalities required to deliver such care plans. In short, the number of commercially vended products with the potential to deliver components of the NOHARM bundles is large and continues to increase. Therefore, our efforts to disseminate the NOHARM intervention will not only target EHR developers and vendors, but also commercial software developers whose products are designed to integrate with and augment that capabilities of EHRs.

The NOHARM content required to replicate NOHARM intervention for clinical delivery includes a range of components, all of which can be readily stored and easily downloaded from the a website. The components include all PRO items, an ePRO flowsheet for item presentation sequence, ePRO item response options with linkages to sets of randomly reoccurring response-specific messages (alerts, reinforcements, reassurance, etc.), patient- and clinician-facing graphic use interfaces. A majority of vendors offer a range of software packages that, in addition to incorporating the elements listed above, can be easily specified with the reporting and algorithmic capabilities integral to the NOHARM intervention coupled with data-triggered alert thresholds. Much content can be downloaded and directly integrated into available software, however other elements will require programing by provider organization to reproduce the NOHARM specifications. We will develop a guide for prospective programmers that includes precise details regarding the specifications required for each bundle component including data repository and web pages. In addition, we will outline strategies to tailor the system for the unique requirements of specific populations and settings.

The overall goal is to make dissemination of the electronic platform elements of NOHARM intervention effective by enabling vendors to adapt NOHARM for use in other health care systems both via EHRs, and, potentially, using other vended solutions. Prospective e-monitoring platform vendors will be able to use a wide range of healthcare and other data standards, including REST architectures and the latest Web services standards, including XML, XPATH, XSLT, SAX, SOAP, and DTDs (document type definitions) and schemas. The patient- and clinician-facing graphic user interfaces utilized in the NOHARM intervention will have well documented APIs that will enable vendors to simplify integrating them into the front end app or web site. Similar design strategies and a well-documented API will be used for secure connections to the back end databases. This project will work with vendors to help them utilize and share plug and play components with the website to help ensure effective dissemination. We are aware that not all clinicians and patients have sufficient access to high bandwidth connections, so a key constraint of the design will be to minimize bandwidth requirements.