

Non-Pharmacological Options in Postoperative Hospital-based and Rehabilitation Pain Management: The NOHARM Trial

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**NON-PHARMACOLOGICAL OPTIONS IN POSTOPERATIVE
HOSPITAL-BASED AND REHABILITATION PAIN MANAGEMENT:
THE “NOHARM” TRIAL**

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1 PRÉCIS

1.1 Study Title

Non-pharmacological Options in postoperative Hospital-based And Rehabilitation pain Management: the NOHARM trial

1.2 Objectives

The study objectives are 1) to test the impact of the NOHARM intervention on pain and function 3 months following surgery, 2) test the impact of the NOHARM intervention on anxiety and opioid use during the 3 months following surgery.

1.3 Design and Outcomes

This is a pragmatic clinical trial using a cluster randomized stepped wedge design. Clusters are defined at the level of care teams and qualifying surgical procedures, and have been randomized to one of five different tranches to implement the intervention at staggered intervals. (See diagram in section 6 “Study Design”).

1.4 Interventions and Duration

The intervention being tested (i.e. compared to usual care/no intervention) is a bundled Healing after Surgery Guide + clinical decision support intervention embedded within the electronic health record. Participants undergoing qualifying surgeries at participating sites will be “on-study” beginning with their decision to have a surgical procedure and continuing until final outcomes are collected at 3 months post-surgery.

1.5 Sample Size and Population

All Mayo Clinic patients receiving one of the surgical procedures included in the NOHARM study will be enrolled in the NOHARM trial. Based on surgical volumes from 2018 and the number of patients required for sufficient statistical power, we plan to enroll 114,000 patients into the NOHARM trial.

2 STUDY TEAM ROSTER

2.1 Principal Investigators

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Mayo Clinic Florida, Jacksonville, FL
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Mayo Clinic Health System – Eau Claire, Eau Claire, WI

Mayo Clinic Health System –La Crosse, WI

** For the purposes of the initial IRB approval, the study has received institutional approval from Dr. Amy Williams, Executive Dean of the Practice and Chair of the enterprise Mayo Clinic Clinical Practice Committee. This approval assumes that all Mayo Clinic surgical practices will participate in the study as an institutional priority, but provides that practice-level approvals will be formally solicited. To obtain these practice-level approvals, the principal investigators have been conducting meetings with practice chairs, specialty councils, and allied health leadership. All IRB approvals have been obtained for clusters within tranche 1, and meetings have begun for subsequent tranches. Obtaining these approvals in advance will ensure that cascading communications can occur in a timely manner. Practice administration for specific surgical practices, providers, and allied health staff implicated in each wave of study implementation will be engaged generally no sooner than 3 months prior to the anticipated start date of the implementation wave they have been randomized to. Engagement earlier than 3 months before study implementation will most likely be counterproductive.*

4 STUDY OBJECTIVES

4.1 Primary Objective

To test the impact of a bundled NOHARM Healing after Surgery Guide + clinical decision support intervention embedded within an EHR on pain and function 3 months following surgery.

4.2 Secondary Objectives

To test the impact of a bundled NOHARM Healing after Surgery Guide + clinical decision support intervention embedded within an EHR on anxiety and opioid use during the 3 months following surgery.

5 **BACKGROUND AND RATIONALE**

5.1 **Background on Condition, Disease, or Other Primary Study Focus**

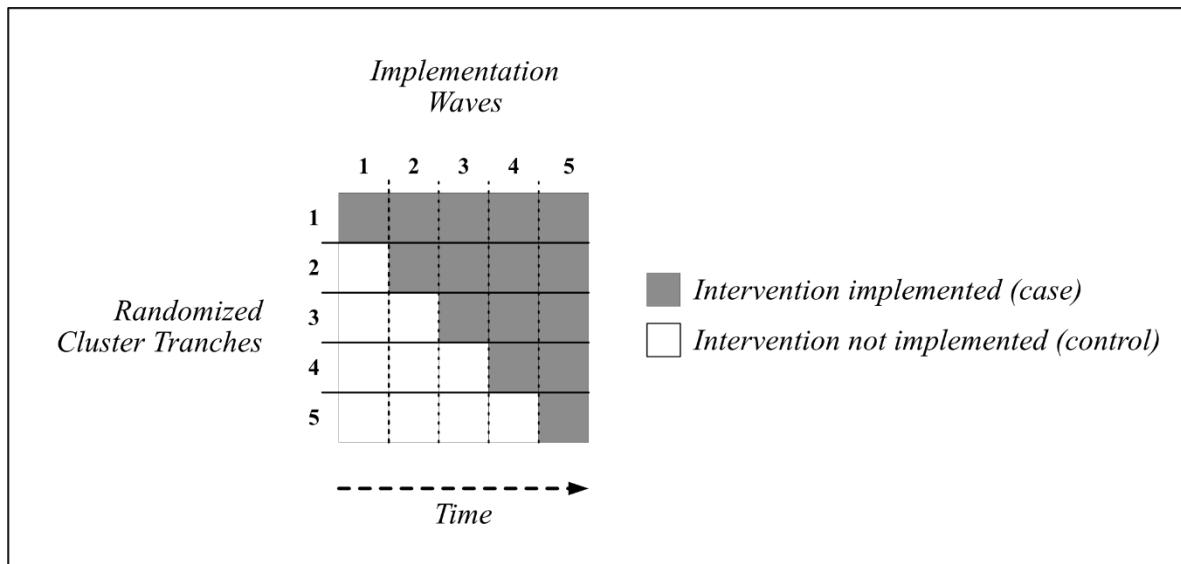
Prescriptions for narcotic pain relief after surgery result in unintended prolonged opioid use for hundreds of thousands of Americans.^{1,2} That trend fuels an excess supply of opioids that can lead to dependence, addiction, diversion, and overdoses on a national scale.³⁻¹⁰ Non-pharmacological pain care (NPPC) is effective and recommended by guidelines for perioperative pain while offering a more favorable risk-to-benefit ratio.¹¹⁻¹⁴ Additionally, patient and clinician decision support interventions are effective in encouraging patient-centered and guideline-concordant care in many other areas of medicine and hold great promise for promoting and facilitating post-operative non-pharmacologic pain management.^{15,16}

5.2 **Study Rationale**

Nonpharmacological pain care is rarely used as first or second-line therapy after surgery, despite guidelines to the contrary.^{17,18} NPPC offers a more favorable risk-to-benefit ratio than opioid medications which may play a critical role in acute post-operative management but should be tapered in favor of safer and more sustainable analgesic options as patients transition home and gradually resume their life roles. Additionally, patient and clinician support interventions have not been tested pragmatically as a bundle in everyday postoperative care as a means of facilitating the uptake of non-pharmacological pain management strategies in the perioperative setting and in the post-acute recovery timeframe. This study will address this knowledge gap and test the impact of utilizing patient and clinician decision support tools to inform patients and facilitate their preference for non-pharmacological pain management modalities.

6 STUDY DESIGN

This study will utilize a cluster randomized stepped wedge design. Clusters are defined at the level of care teams and qualifying surgical procedures, and have been randomized to one of five different tranches to implement the intervention at staggered intervals (one new cluster each wave, see diagram below).



The primary outcome of the study is a composite of patient reported pain and function at three months post-surgery. This will enable us to determine the effectiveness of a bundled NOHARM Healing after Surgery Guide + clinical decision support for promoting non-pharmacological pain management strategies to patients undergoing qualifying surgeries, which may also ultimately curb overall patient demand for opioid prescriptions in post-acute post-surgical rehab while optimizing functional recovery. Thus, our secondary outcome(s) is opioid use at the 3 month point post-operatively. This will enable us to understand the impact of our EHR-embedded decision support intervention in an era where opioid prescribing is already being constrained.

All patients receiving common, pre-defined procedures within 7 surgical practice areas at 6 Mayo Clinic locations will receive the study intervention if their surgery date coincides with the stepped wedge implementation schedule. Study locations include Mayo Clinic Rochester, Mayo Clinic Florida, and Mayo Clinic Arizona, as well as three Mayo Clinic Health System sites (Mankato, MN; La Crosse, WI; and Eau Claire, WI). Surgical practice areas will include orthopedic surgery, colorectal surgery, gyn surgery, obstetrics, pulmonary/thoracic surgery, liver and kidney transplant, and cardiac surgery. Due to variable combining of post-op unit care areas, practice size, and related considerations we have formed 22 clusters that will be randomized across 5 tranches.

Enrollment in the intervention arm of the trial will extend from March 2021 to approximately August 2023. Participating practices will be enrolled in the study from the point in time the intervention is implemented in their practice and continuing through the end of the study.

The intervention consists of enhanced electronic medical record functionality that interfaces with a patient-facing Healing after Surgery Guide in Epic *MyChart* patient portal. The Healing after Surgery Guide encourages patients to make a plan for post-operative pain management and to utilize NPPC techniques that appeal to them. The intervention also uses EHR tools that remind and prompt clinicians to encourage patients to use their selected NPPC techniques throughout the perioperative period. All study assessments will be extracted from the electronic health record. Patient reported outcome measures will include those collected in routine peri-operative care, as well as a limited number specific to the NOHARM trial; self-reported opioid consumption and NPPC modality use after surgery.

7 SELECTION AND ENROLLMENT OF PARTICIPANTS

7.1 Inclusion Criteria

All patients 18 years of age and older undergoing qualifying surgeries at participating sites will be eligible.

7.2 Exclusion Criteria

None.

7.3 Study Enrollment Procedures

All eligible patients at participating sites will be enrolled in this minimal risk, population-based study. An automated EHR-based algorithm will identify patients meeting inclusion criteria for the NOHARM study based on age, surgical procedure, clinical department, and location.

Eligible patients in not-yet activated clusters will receive usual care; data collected from this group will serve as “control” data in this stepped wedge study. Control state data will be collected prior to cluster activation.

All patients scheduled for surgery; as well as their care surgical teams, physical and occupational therapists, and unit nurses, in activated practice clusters will be exposed to the intervention per the randomization scheme. Because the intervention is embedded in the EHR, patients who are unable to interact with the portal-based Healing After Surgery Guide will not provide the data needed to populate and drive the EHR-based algorithms and clinical decision support tools. Therefore, these individuals will be less exposed to the intervention. However, the patients who do not interact with the Healing after Surgery Guide via the EHR patient portal prior to their hospital admission¹ will have the opportunity to select NPPC modalities during their hospitalization, both pre- and post-operatively. By communicating their NPPC selections to their unit nurses, their preferences will be entered into the EHR via flowsheets. Subsequently, all EHR clinical decision support functionalities to encourage NPPC use will be operational for these patients. Cognitive limitations, lack of English fluency, or psychiatric illness may result in an inability to use the Healing After Surgery Guide which may also result in reduced exposure to the intervention.

8 STUDY INTERVENTIONS

8.1 Interventions, Administration, and Duration

Once the NOHARM intervention is activated at a given participating site, patients undergoing qualifying surgical procedures will be exposed to the NOHARM intervention.

The intervention includes:

Healing after Surgery Guide:

The Healing after Surgery Guide is an interactive module in the Mayo Clinic patient portal (MyChart). Entry of an order for their surgery will trigger an EHR algorithm will automatically send a message to patients' portals describing the need for an "individualized pain management plan to promote healing after surgery." The portal message will provide a link allowing patients to access and engage with the HAS Guide before their surgery. The HAS Guide will encourage realistic expectations about post-surgical pain, will educate patients on several evidence-based, non-pharmacological pain management strategies (which are robustly validated and endorsed in clinical guidelines), and will encourage patients to select the NPPC modalities that appeal to them in managing post-acute pain during the months following their discharge. Patient selections elicited via the Healing After Surgery Guide will prompt a follow-up portal message, acknowledging the patient's NPPC selections and extending the opportunity for them to receive a printed Healing After Surgery workbook if they request that such resources be mailed to them. Patients will have the opportunity to receive portal messages based on their responses to the Healing After Surgery Guide and PROMIS CAT (standard of care) as well as based on the length of time from surgery. These messages will include direction on how they can access the website, join Zoom support calls if desired or contact the NOHARM team. Section 8.1.1 gives a break down of the possible portal messages. The Zoom support calls referenced in the portal messages are to assist patients with their selected modalities if they so wish. Patients will log into these calls anonymously and PHI will not be discussed. There will be calls that center around specific modalities as well as open Q&A style.

EHR-based Clinical Decision Support:

The NPPC selections will be stored in the EHR and used to prompt perioperative clinician interactions, direct education delivered by unit nurses, inform modality choices during physical and occupational therapy sessions, and populate patients' pain management plans for controlling pain following hospital discharge.

Additionally, patients' NPPC selection will be visible to clinical providers on the Epic inpatient Summary view. These components are considered standard of care.

Mayo Education Material:

A suite of self-management educational materials will be available to support patients' use of NPPC modalities and to help them trouble shoot and refine the use of their selected modalities. These print materials and videos provide information

and instruction on the safe and appropriate use of NPPC strategies for addressing post-surgical, post-acute pain. The materials additionally clarify how patients may adapt NPPC modalities to derive optimal benefit given their unique requirements and post-surgical precautions. All education materials have been developed, vetted and approved through Mayo Clinic's Office of Patient Education processes and reflect existing standard of care for patient education. These materials will be available to patients via the Healing After Surgery website (healingaftersurgery.mayoclinic.org) and on Mayo Clinic Television. Brief video descriptions of the NPPC modalities are imbedded in the Healing After Surgery Guide. The materials include video and print resources, with the latter being available in both electronic and paper formats. The materials offer informational, instructional, and guided experiential content for all NOHARM NPPC modalities, as appropriate. A Healing After Surgery Workbook is also available. The workbook offers patients a location to record their experiences, concerns, and successes, as well as providing motivational messages.

Patients may view the self-management educational materials during their hospital stays on Mayo Clinic television. Based on patients' NPPC modality selections, inpatient nurses will be prompted to show patients how to navigate to the materials on Mayo Television, familiarize them with the Healing After Surgery website, and provide them with print materials if desired. Nurses will also use the educational materials to discuss pain management planning with patients to refine their management plans following hospital dismissal.

The materials will be available on a website, DVD, and Mayo Clinic TV. Unit nurses will be able to give patients printed PDFs, as required. Additionally, patients will receive a copy of the Healing After Surgery workbook via mail after they are enrolled onto the study. They will also have the ability to request from their portal messages that a print copy of the workbook be mailed to them.

See [Section 8.1.1 NOHARM Resource List](#) for a brief description of the NOHARM materials

Perioperative live NPPC Support Resources

Patients have the opportunity to engage with Mayo Clinic specialists in NPPC modalities perioperatively to support their selection, troubleshooting, and use of the modalities. Patients are notified of live support resources through their patient portal upon completion of the Healing After Surgery guide and are given a RACK card distributed at the pre-operative consultation. This support is restricted to NPPC modalities and patients are clearly informed that any questions relating to medications and other analgesic approaches should be directed to their surgical care teams. This support is set up to maximize the patient's successful self-management of the NPPC both pre and post operatively. NOHARM NPPC live support will take the forms:

1. Toll free call for 1-on-1 discussion of individualized needs. 1-833-919-1432
2. Presentations and group discussions via a virtual platform (Zoom technology).

See [Appendix B NOHARM Resource List](#) for a brief description of the NOHARM materials

Clinical team decision support:

Patient NPPC modality selections elicited from the Healing After Surgery Guide will be converted to discrete data elements that will prompt clinician decision support (CDS) after surgery. CDS tools that promote preference-sensitive, guideline-concordant NPPCs at defined touchpoints on the perioperative care trajectory will encourage clinicians, nurses, and physical/occupational therapists to discuss NPPC modalities with patients and pre-populate fields and functionalities within Epic such as the “After Visit Summary”.

See [Section 8.1.1 NOHARM Resource List](#) for a brief description of the NOHARM materials

8.1.1 NOHARM Resource List – Found in Appendix B

8.2 Handling of Study Interventions

The NOHARM interventionHealing after Surgery will be assigned to patients using an EHR Boolean logic-based algorithm that includes age, surgical procedure, clinical department, and location. The intervention will be delivered to patients and their care teams via the patient portal and EHR, respectively. For some patients, we may send paper versions of the pain and physical function PROs to the patients at the 1, 2, and 3 month post-op points. If the patient receives and completes duplicate versions, the one time stamped earlier will be used for analysis.

8.3 Concomitant Interventions

This is a pragmatic, population-based clinical trial. All eligible patients undergoing qualifying surgical procedures who receive care at the 6 participating sites will be enrolled, regardless of medications, treatment, supplements or other interventions they may be taking/receiving.

8.3.1 Allowed Interventions

The interventions in this study are a patient-facing “Healing after Surgery Guide” and a clinical team-facing clinical decision support augmented by existing, vetted patient education materials already consistent with the scope of work for perioperative care. These interventions could prompt utilization of NPPC modalities prior to, during, and after the hospital stay.

8.3.2 Required Interventions

Among collaborating practices, Healing after Surgery Guide functionality and clinical decision support components of the intervention bundle will be turned on according to the pre-specified randomization scheme. How or

whether patients and care teams choose to interact with the various intervention components and resources will be at their discretion. The NOHARM intervention is conceptually distinct from the index surgical procedures for which patients are scheduled, which, though temporally associated, are not considered part of the research intervention.

8.3.3 Prohibited Interventions

None. We do not have the ability to individually turn off the intervention for individual patients, though records of patients who have previously indicated they do not want their medical record used for research purposes will have data associated with their care redacted from final analytic datasets.

8.4 Adherence Assessment

Patients will be encouraged, but not required, to interact with the NOHARM Healing after Surgery Guide and to utilize suggested NPPC modalities.

Additionally, patients who are unable or unwilling to interact with the portal-based Healing After Surgery will not provide the NPPC selection 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 Healing After Surgery Guide during day-of-surgery intake and post-operative care processes, but this may not occur due to many competing demands, or patient preferences.

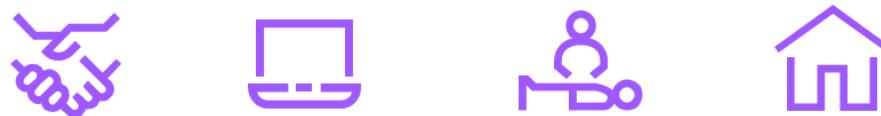
Cognitive limitations, lack of English fluency, or psychiatric illness may result in inability to use the HAS Guide or complete the electronic patient reported outcome measures (ePROMs).

Interaction with the NOHARM HAS Guide, completion of ePROMs and utilization of NPPC modalities will be assessed by time-stamped links associated with the Healing after Surgery Guide while ePROMs and NPPC modality use will be extracted from the medical record.

9 STUDY PROCEDURES

9.1 Perioperative Care Pathway/NOHARM Touchpoints

The figure below briefly summarizes the perioperative care pathway along which our bundled, EHR-based intervention will be implemented.



Choosing Surgery

Ambulatory care team members prepare patients to engage with the NOHARM intervention and a portal-based decision tool.

Pre-operative Planning

Patients review non-pharmacologic pain management options and inform care team of selections via portal-based decision tool.

The Inpatient Stay

Inpatient staff notice, acknowledge, discuss, and support provision of non-pharmacologic pain management modalities.

Post-operative Recovery

Patients continue to access and use non-pharmacologic pain management resources and modalities.

9.2 Description of Evaluations

9.2.1 Choosing Surgery and Pre-Operative Planning Touchpoints

Touchpoint 1- Choosing Surgery

Ambulatory care team members prepare patients to engage with the NOHARM intervention (portal-based Healing after Surgery Guide) at the time surgery is scheduled.

Touchpoint 2 – Pre-operative Planning

Patients interact with the Healing after Surgery Guide via their Epic EHR MyChart portals. The Healing after Surgery Guide will allow patients to select NPPC techniques that appeal to them and develop an individualized NPPC plan. Patients will be encouraged to familiarize themselves with and practice NPPC modalities prior to their hospital admissions. Additionally, they will be encouraged to obtain needed supplies, engage their caregivers, and even schedule appointments with NPPC practitioners prior to their hospitalizations so that their individualized pain management plans may be seamlessly transitioned from the hospital to the home or post-acute care setting.

9.2.2 Inpatient Stay Touchpoints

Touchpoint 3 – Acute Hospital Care

Nursing and physical/occupational therapy staff will offer patients the opportunity to receive preference-concordant NPPC modalities during their

hospital stay. For self-administered practices, staff will validate patients' preferences and ensure the availability of needed supplies, instruction and ambient conditions (e.g. privacy).

If patients are not experiencing adequate pain relief, they will be prompted by nurses to try alternative NPPC modalities in order to raise awareness of opioid harms, and enhance clinician support for patients' NPPC use. Additionally, NPPC nurse and physician specialists will be "on call" to assist unit nurses, therapists, and members of the surgical care team in how to optimize the safety and effectiveness of NPPC modalities for specific patients.

Touchpoint 4 – Hospital Discharge

During the discharge process, patients will be asked to revise their NPPC plan, as needed based on their preferences and responses to specific NPPC modalities, and provided with support and resources. Discharge planning will include facilitation of continuation of patients' NPPC use in their post-acute care settings (e.g. home, rehabilitation facility, etc.). Patients will be given prescriptions to receive local NPPC, if available and/or appropriate.

Patients' discharge summaries will be auto-populated with selection-concordant NPPC instructions and resources to find local NPPC providers.

9.2.3 Post-Hospital Discharge Recovery Touchpoints

Touchpoint 5 – Remote Healing After Surgery Guide Use and Post Operative Follow-up

Patients will be encouraged to use the Healing After Surgery and follow their individualized pain management plans during their post-surgical recovery. They will be asked to report on their pain intensity, anxiety, and limitations in physical function using PROMIS ePROs via the Epic MyChart patient portal. Patients will, at the same time points, be asked which, if any, of the NPPC techniques they have used and at what frequency. These measures will be collected at 1 month, 2 month and 3 months post surgery. In addition, at the 3 month timepoint the patient will be asked to self-report opioid use measures.

Include here which responses will trigger which messages.

Additional Triggered Touchpoints

Opioid Refill Requests

Opioid refill requests during the 3-month postoperative interval will trigger messaging via the patient's portal with information regarding how to access resources to support their NPPC use. Patients will be encouraged to utilize the live support resources, particularly the 1-on-1 calls in order to select and adapt use of modalities for optimal benefit.

10 **SAFETY ASSESSMENTS**

This is a minimal risk study. Participants are considered “enrolled” as soon as they meet study inclusion criteria and are automatically assigned to receive study interventions and/or measurements.

10.1 Specification of Safety Parameters

There are no pre-specified safety parameters, as they are not-applicable to the intervention being studied. This study engages patients in strategies for post-surgery pain management that conform to guideline-based care, all of which have far lower risk profiles (almost zero risk) and greater benefit-to-risk ratio compared to usual post-surgical pain management that involves opioid medications. Patients whose pain cannot be sufficiently managed with non-pharmacological pain management strategies will be supported by their surgical team (with assistance from pain management clinicians, as needed) using conventional pain management strategies.

10.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Our interventions are informational and logistical and designed to enhance safe, patient-centered approaches to patient care. If they were to prompt, for instance, less opioid use, in theory, that could lead to worse function or increase pain. That is why we chose the composite outcome measure of pain and physical function. Whether it is accurate to associate that “risk” to our intervention itself, versus the treatments prompted by our intervention is a topic of debate. Nevertheless, this is a minimal risk study. If we conservatively assume that downstream prescribing practices are attributable to our interventions, usual care (using opioid medications as a first line approach to pain management in the acute and post-acute recovery periods following a surgical procedures) introduces greater risk of dependency, addiction, and overdose, than those posed by the intervention we are providing in the NOHARM trial which is guideline concordant.

10.3 Adverse Events and Serious Adverse Events

Adverse Event (AE): Any untoward or unfavorable medical occurrence resulting unambiguously from the misuse or overuse of non-pharmacological pain management strategies facilitated by the intervention. All untoward or unfavorable medical occurrences will be first assumed to be associated with the patient’s surgery. Untoward or unfavorable medical occurrences will be deemed an adverse event only if they can be clearly associated with use of non-pharmacological pain management strategies recommended and/or facilitated by the intervention and could not, under any circumstances, have otherwise happened.

Serious Adverse Event (SAE): Any adverse event unambiguously associated with the intervention that:

- Results in death

- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

There are no laboratory or other clinical values which may be used to assess safety concerns related to the intervention. Patient reported pain, requests for assistance with pain management, and other health outcomes, while measurable, are associated with the patient's surgical procedure and will be gathered as part of the ultimate outcome data. If patients were to experience a paradoxical response to a modality –massage, for example – those effects would likely be transient and they would have access to all the usual care resources of Mayo Clinic as any other patient should those symptoms persist.

Adverse events that may be anticipated in the study involve any patient misuse or overuse of non-pharmacological pain management strategies. Patients who elect to incorporate non-pharmacological pain management strategies in their recovery from surgery will be instructed in the use of those strategies, including whether (and when) the use of those strategies is appropriate in their situation.

Because non-pharmacological pain management modalities recommended by the intervention are guideline concordant approaches to pain management under normal circumstances, they will be monitored by the patient's surgical team as a part of usual post-acute care. Therefore, we will not actively review for potential events with scheduled promptings.

Unprompted adverse events are possible, but not expected. Surgical teams will inform the study team if they are made aware of any untoward medical occurrence that could reasonably be attributed to a patient's misuse or overuse of non-pharmacological pain strategies as a direct result of the facilitation provided by the NOHARM intervention. Such events are highly unlikely, and the risks of such events leading to unfavorable outcomes is almost non-existent. The risks of participant cooperation in the NOHARM intervention is far less than the risks of usual care which often involve opioid medications alone in the acute and post-acute recovery periods.

10.3.1 Reporting Procedures

An AE or SAE will be suspected if a member of the patient's surgical team or any member of the study team who interfaces with the patient for any reason suspects that a patient is experiencing a medical issue that is unambiguously related to the patient's interaction with the NOHARM intervention.

The principal investigator, relevant study team members, and any relevant members of the surgical team will adjudicate the relevance of the patient's experience to the NOHARM intervention (versus an anticipated result of the patient's surgical procedure).

If a patient experience or outcome is determined to be an AE or SAE by protocol definition, then that patient's experience will be documented and reported per institutional procedures. The surgical team and/or members of the study team with expertise in post-surgical pain management will follow up with that patient to ensure that appropriate steps are taken to mitigate any negative outcomes and ensure that the patient is properly informed and educated about safe use of non-pharmacological pain management strategies for the remainder of their surgical recovery.

Severity of the Event

All AEs will be assessed by a qualified medical professional using a protocol defined grading system.

Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.

Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to the Study Intervention

Because this is a minimal risk study and the intervention may be construed as less risky than usual care, it would be inappropriate to regard the study intervention as suspect, by default, for all medical occurrences in the perioperative period. For this reason, the principal investigator, clinical experts on the study team, and the patient's surgical team will adjudicate the relevance of patient events outcomes in a binary fashion:

- Not related to the NOHARM intervention. This will be the presumption, unless proven otherwise. Patients may be expected to have many challenges to overcome following a surgical procedure. These challenges are unrelated to the intervention.
- Related to the NOHARM intervention. The study team will evaluate all occurrences suspected of being associated unambiguously with the NOHARM intervention and adjudicate their relevance. We do not expect any AEs or SAEs to result from the NOHARM intervention.

10.3.2 Follow-up for Adverse Events

Patient events suspected of being AEs or SAEs will be addressed immediately by the Principal Investigator, relevant experts on the study team, and/or the patient's surgical team. Upon determination that an event is indeed an AE or SAE, appropriate actions will be taken, including contacting the patient and providing instructions.

All events suspected of being AE will be documented, and documentation for recorded events subsequently determined to be an AE or SAE will be updated. All AEs and SAEs will be followed to adequate resolution.

The study coordinator will record all events reportable by the definitions above occurring any time following patient enrollment and limited to the last data collection point in the study. All events are expected to occur in the acute or early post-acute periods of recovery.

10.4 Safety Monitoring

The Data and Safety Monitoring Board and/or Safety Officer appointed by the NIA will monitor the conduct of the study.

11 **INTERVENTION DISCONTINUATION**

This study is a pragmatic clinical trial, and as such, patients will not be individually consented. However, voluntariness is preserved as patients and surgical teams are not required to engage with any component of the intervention they are not interested in or deem irrelevant to their care. Additionally, as a pragmatic clinical trial, “the intervention” will be systematically implemented at the surgical practice level, per the stepped-wedge schedule, as an element of usual care.

Therefore, discontinuation of the study, whether for an individual participant or for all participants at once is defined as the cessation of study measurement prespecified by the study timeline. The discontinuation of the study intervention components, if merited, will be at the discretion of the surgical specialties in conjunction with the DSMB; discontinuation is not anticipated.

Removal individual patients from the trial will be functionally achieved in the following situations:

- The patient actively requests to have their records withdrawn from the NOHARM study dataset. This is unlikely, as patients will only know of NOHARM as a practice-based care initiative per the pragmatic design of the trial.
- Patients previously indicating their unwillingness to have medical record data used for research purposes will have their records redacted from final study datasets prior to analysis.

Cessation of study measurement will happen for the entire trial in the event that:

- Institutional needs / priorities preclude our ability to conduct study procedures (e.g. in the case of institutional response to COVID-19).
- The study funder requests that study activities cease.

In the event that an individual patient withdraws from the study or the entire study ceases, patients will still be monitored by their surgical team per usual care practices for the duration of their post-acute recovery period. Cessation of study procedures will not impact patients’ access to standard supportive care following surgery.

12 STATISTICAL CONSIDERATIONS

12.1 General Design Issues

This study will address the primary objective using a cluster randomized stepped wedge design. Surgical practices, or clusters, will be randomized in 5 tranches to receive the NOHARM intervention; outcomes of patients treated by these teams will be compared by intervention status of the team. The primary statistical hypothesis is that pain and function measures will be lower and higher, respectively, in the patients treated under the intervention conditions, when compared with non-intervention patients in those same practices.

The cluster randomized stepped-wedge design will allow us to stagger the NOHARM implementation while increasing statistical power. The alternative to staggering the implementation would be to implement at all sites at the same time, which is impractical from a resource perspective. The stepped-wedge design allows each site to serve as its own control, reducing 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 22 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.

The primary hypothesis is that the NOHARM intervention will reduce patient reported pain and increase patient reported function following designated surgical procedures relative to patients treated under usual care. The primary outcome – a composite of patient reported pain and function – 3 months post-operatively will be assessed using validated patient reported outcomes.

12.2 Sample Size and Randomization

Using pain data for 6,261 patients with these procedures at six sites, we estimated the intra-cluster correlation coefficient (ICC) for the pain score to be modest $\rho = 0.037$. To assess minimal detectable effects, we simulated a large number of randomizations and estimated the detectable effect for each. Specifically, for $P = 1, \dots, 5000$ permutations, the 22 clusters were randomly assigned to 5 waves. For each permutation, the closed form solution of Harrison et al (2019) was used to estimate $SE(Q)$ (derived from the formula of Hussey, Hughes (2008)) for true effect Q . We used the values $\sigma^2 = 1$ and $\tau^2 = 0.488$ for the within and between variance components so that detectable effects would be in SDs, and assumed ICC would be 0.037. Over the 5,000 permutations, the detectable effect ranged between 0.048SD and 0.055SD.

12.2.1 Treatment Assignment Procedures

In order to balance cluster characteristics, we applied a constrained randomization procedure. Constrained randomization allows us to balance a larger number of cluster characteristics than is possible through

stratification. Here the key cluster characteristics to be balanced were: site (6 locations), volume (estimated using 2018 data), procedures (3 groups), and number of teams (1-4). Given only 22 sites, it would not be practical to stratify or apply minimization, while constrained randomization allows us to select an allocation of sites to waves from among a set of allocations that has better balance on these factors.

Specifically, we generated 100,000 allocations of the 22 clusters to 5 waves. For each allocation, we then calculated a balance metric B as follows. For each characteristic c listed above, let $X(c)_i$ be the value of c for each cluster $i=1,\dots,22$. For categorical factors X is an indicator, for volume and number of teams X is a number, rescaled to range from 0-1. Let $w=0,\dots,5$ be the baseline ($w=0$) and 5 intervention waves; and for a given allocation, let S_i = the first wave at which cluster i is allocated to intervention. Then we calculate for each allocation the balance metric

$$B = \sum_{w=0,5} (\bar{S}_i - w) \left| \sum_c X(c)_i (S_i \leq w) - \sum_c X(c)_i (S_i > w) \right|$$

After generating 100,000 allocations, we constrained selection to those with values of B in the lowest decile; we then selected one allocation randomly from those 10,000 ‘acceptable’ allocations. This process resulted in a full allocation of all 22 sites to waves 1-5 prior to initial intervention.

12.3 Interim analyses and Stopping Rules

This is a minimal risk study for which there is no planned interim analysis. Interim analysis may be conducted at the request of the DSMB or if necessitated by unforeseen changes in the study plan (e.g. loss of a study site). Similarly, there are no pre-specified stopping rules as the probability and magnitude of adverse experiences are not greater than those ordinarily encountered in daily life.

12.4 Outcomes

Outcomes will be collected via the Epic EHR. PROMs will be collected using interfaces available to patients in their MyChart patient portals or the Welcome tablet functionality at point of care as available. Because outcomes will be either PROMs or data entered by providers during routine care delivery, requirements for adjudication will be minimal. Health care utilization is an exception in that criteria for hospitalizations vary based on designations of observational status. The NOHARM Data Management working group will identify hospitalizations that may require adjudication, including ER stays that exceed 24 hours. A committee blinded to a patient’s affiliation with an activated or control cluster will determine whether to designate such instances as hospitalizations.

The cadence and mode of PROM data collection are outlined below. PROMs comprise the NOHARM trial’s co-primary and a majority of its secondary outcomes. PROMs will additionally be collected for use in describing the study population and for analytic adjustments.

12.4.1 Primary outcome

Physical function and pain interference, as measured with the Patient Reported Outcome Measurement System (PROMIS) computer adaptive tests (CATs) are the co-primary outcomes. The CATs in the Mayo Clinic Epic EHR have been parameterized with stopping rules based on number of items administered rather than a standard error of measurement-defined threshold. IRT-based instruments have generally better discrimination across the entire trait range than legacy PROMs,^{19,20} and CAT administration enhances measurement efficiency and precision.^{21,22} The PROMIS item banks have been validated in the target populations.²³⁻²⁵ The PROMIS physical function and pain interference CATs will be assigned via an automated Epic function precisely 3 months following each patient's surgery. Patients will receive an automated reminder message via their patient portals prompting them to complete the PROMs.

Because post-operative visit requirements and sequences vary across surgical practices, administration of the PROMIS CATs will not be linked to a specific visit, but rather assigned automatically after 3 months have elapsed since surgery. If this data coincides with a clinic visit, then patients will be encouraged to complete the PROMIS CATs via the Epic Welcome interface using a tablet in the waiting room prior to their clinic visit.

12.4.2 Secondary outcomes

Secondary outcome measures will include opioid consumption, NPPC use, healthcare utilization and anxiety. Anxiety will be measured in a manner similar to physical function and pain interference with a PROMIS CAT administered via the Epic MyChart portal or the Welcome tablet interface prior to a clinic visit that coincides with the 3-month post-surgical time point.

Opioid consumption will be collected using three methods. First, opioid consumption per hospital day, will be extracted from the medication administration log in the EHR. As in previous work,²⁶⁻²⁸ parenteral, transdermal, and oral opioid consumption will be expressed as oral morphine equivalents (OMEs). Second, oral and transdermal opioids prescribed by a Mayo Clinic provider at the time of hospital discharge and during the interval between hospital dismissal and the 3 month post-surgical assessment point will be extracted from the EHR and converted to OMEs. Last, because outpatient prescriptions do not accurately capture opioid consumption, patients will be queried at the 3 month post-operative time point regarding their opioid use using a subscale from a validated opioid consumption questionnaire.²⁸

NPPC use will be collected using two methods. First, the frequency with which patients use specific NPPCs during their hospital stays will be

extracted from Epic flowsheets. Nurses, as well as occupational and physical therapists record delivery of modalities as well as education regarding modalities in Epic flowsheets. This information will be electronically extracted and expressed as count data. Second, patients' use of NPPC modalities will be assessed using self-report. At the 1-, 2- and 3-month assessment point patients will be queried regarding which of the NOHARM NPPC modalities they have used since hospital discharge. The will be presented with a list of the NOHARM modalities and asked to indicate those that they have used. Epic cascading logic will then present a second item for each modality that a patient has used which will ask them "How many times per week, on average, do you use *modality*?" 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.

12.5 Data Analyses

Because patients are randomized in clusters, all statistical methods will account for potential correlation of measures within clusters. Such methods include cluster adjusted standard errors for t-tests and χ^2 -tests, and mixed effects models. Patient characteristics will be summarized by intervention status, and tested for difference between intervention groups; any factors which are imbalanced will be accounted for in the main analyses. Factors assessed for balance and potential inclusion in pre-specified analyses are those listed in Section 13.1.1 and all baseline measures listed in 13.1.2.

The primary and secondary outcomes will be compared between intervention groups using mixed effects generalized linear models. Each model will include an indicator for intervention group; a random intercept for cluster; cluster level factors that were used to constrain randomization; calendar time; surgery type; and any patient factors that were imbalanced across groups.

The model details for each outcome are as follows:

1. PROMIS CATs (anxiety (1°), physical function (1°), pain (1°)). These are continuous measures, collected at two time points, pre-operative and 3 months post-operative. To assess the impact of the intervention on these we will estimate three separate models. If Y_{ijt} is the measure at time $t=1,2$ of the i th patient treated by the j th cluster, then we will estimate

$$Y_{ij2} = \beta_0 + \beta_I I_{ij} + \beta_B Y_{ijo} + \beta_T T + \mathbf{B}_X \mathbf{X}_{ij} + \mathbf{B}_Z \mathbf{Z}_j + u_j + e_{ij} \quad (1)$$

where I_{ij} indicates the intervention status, T is calendar time, $u_j \sim N(0, \tau^2)$ is a cluster level random effect, X_{ij} is a vector of patient characteristics, including surgery type, Z_j is a vector of cluster characteristics used for randomization, and e_{ij} is a residual error. By testing $\beta_I = 0$ we can assess whether the intervention is associated with changes in the corresponding measure.

2. NPPC use. This is collected as a binary value for each of 14 modalities, collected at one time point, 3 months post-operative. We will sum these to create a score, and use a model similar to (1) but without a baseline value Y_{ij0} :

$$Y_{ij} = \beta_0 + \beta_I I_{ij} + \beta_T T + \mathbf{B}_X \mathbf{X}_{ij} + \mathbf{B}_Z \mathbf{Z}_j + u_j + e_{ij} \quad (2)$$

Again by testing $\beta_I = 0$ we can assess whether the intervention is associated with changes in the corresponding measure.

3. Opioid use will be measured using 4 outcomes:

- a. Hospital-based consumption, daily oral morphine equivalents (OMEs). This is a continuous measure for each day of hospitalization; we will assume that this depends in part on the day post surgery, D_{ij} and model

$$Y_{ij} = \beta_0 + \beta_I I_{ij} + \beta_D D_{ij} + \beta_T T + \mathbf{B}_X \mathbf{X}_{ij} + \mathbf{B}_Z \mathbf{Z}_j + u_j + e_{ij} \quad (3)$$

For this model we will consider D_{ij} as first continuous and then as categorical.

- b. Discharge and post-discharge prescriptions, daily oral morphine equivalents (OMEs). For this outcome, we will use a model analogous to (3), where D_{ij} is replaced by number of days post discharge.
- c. Number of post-discharge prescriptions. These are counts for the 3 month period following surgery. The impact of the intervention will be assessed using a model similar to (2) but with a Poisson link function:

$$\ln(E(Y_{ij})) \sim \beta_0 + \beta_I I_{ij} + \beta_T T + \mathbf{B}_X \mathbf{X}_{ij} + \mathbf{B}_Z \mathbf{Z}_j + u_j + e_{ij} \quad (4)$$

$$Y_{ij} \sim \text{Poisson}(\mu)$$

We will assess the distribution first using an empty model, and potentially adopt a zero inflated Poisson, negative binomial, or zero inflated negative binomial according to the corresponding AIC values.

- d. Daily use of opioids; this is binary outcome collected one time, at 3 months post-surgery. To assess the impact of the intervention we will use a model similar to (4) but with a logit link:

$$\text{logit}(Y_{ij}) \sim \beta_0 + \beta_1 I_{ij} + \beta_2 T + \mathbf{B}_X \mathbf{X}_{ij} + \mathbf{B}_Z \mathbf{Z}_j + u_j + e_{ij} \quad (5)$$

For a-d we can again test $\beta_1 = 0$ we can assess whether the intervention is associated with changes in the corresponding measure.

4. Healthcare utilization

- a. Hospitalizations
- b. ER visits
- c. Calls to surgical practice

All three of these are count outcomes, and so we will assess the impact of the intervention using a model similar to (4) above. As with (4), we will compare model specifications using an empty model first to determine the best count family (Poisson, negative binomial, zero inflated or not) using AIC, then apply that in the final model.

12.6 Subgroup analyses

12.6.1 Clinical and Demographic subgroups

Subgroup analyses will be performed for a) separate procedures b) separate age groups c) separate genders and d) separate racial/ethnic groups. Patients will be stratified using each classifier and the primary analyses replicated in each subgroup.

12.6.2 Patients at risk of unplanned prolonged opioid use (UPOU).

Hypothesis: Patients at moderate to high risk for UPOU, defined by score on the pain catastrophizing scale, pre-operative opioid use, and/or chronic pain will use NPPC modalities significantly less frequently than patients who are at low risk of UPOU.

Self-reported use of NPPC, expressed as a binary (Yes/No) response and assessed at 3 month post-surgical time point, will be compared between patient subgroups stratified by UPOU risk.

12.6.3 Patients who are rurally situated.

Hypothesis. Patients who are rurally situated, as defined by US Census Bureau criteria, will use NPPC modalities significantly less frequently than patients who are situated in urbanized areas and urban clusters.

Self-reported use of NPPC, expressed as a binary (Yes/No) response and assessed at 3-month post-surgical time point, will be compared across patient subgroups defined by US Census Bureau urban/rural criteria.

12.7 Supplementary Analyses

12.7.1 Moderators

In supplementary analyses we will assess whether procedure, age, sex, or race/ethnicity moderate the intervention effect. The models (1)-(5) used in the primary analysis will be expanded to include indicators for one of these subgroup classifiers, as well as the interaction with intervention status. By testing whether the interaction effect differs from zero, we can assess whether these factors moderate the intervention.

12.7.2 Mediators

In related supplementary analyses, we will test whether interim patient measures mediate the effect of the intervention on the separate outcomes. We will adapt models (1)-(5) to path analysis, a type of structural equation model, which will allow us to specify an indirect effect (of the intervention through the potential mediator) and test whether it is non-zero.

13 **DATA COLLECTION AND QUALITY ASSURANCE**

13.1 Data Collection Forms

All data points for the NOHARM study will be collected via programmatic extraction from the electronic health record. In addition to demographic, diagnostic, and procedural clinical variables, this includes patient reported outcomes and medication information that are captured electronically from patients as part of routine (i.e. usual) perioperative care at Mayo Clinic.

13.1.1 Clinical and Demographic variables

- Age
- Sex
- Race/ethnicity
- Insurance status
- Procedure
- Zip code of residence (for classification as rural or non-rural residence)
- Comorbidities
 - Elixhauser comorbidity index

13.1.2 Treatment and outcomes variables

The following items will be captured in addition to clinical and demographic variables:

- Patient Reported Medical Information System (PROMIS) computer adaptive test (CAT)
 - Pain interference @ baseline and 1, 2 and 3-months post-surgery
 - Physical functioning @ baseline and 1, 2 and 3-months post-surgery
 - Anxiety @ baseline 3 months post surgery
 - Numerical rating scale pain scores reported q shift during hospitalization
- Pain catastrophizing scale
- TAPS prescription medication use item
- PHQ-4 (four item patient health questionnaire for anxiety (GAD 2) and depression (PHQ 2))
- Opioid prescribing survey
- History of opioids prescribed in one year prior to surgical procedure
- In-hospital administration of medications including oral morphine equivalents and opioid alternatives (i.g., acetaminophen) consumed during

hospitalization

- “Discharge” opioid prescriptions, which may be prescribed prior to the procedure due to clinic workflow
- Opioid prescription orders up to 1 year post-discharge (“refills”)

Data will be programmatically extracted and curated by study team members, including data managers, analysts, and/or statisticians. All data will exist prior to the time of access, and no further patient contact is needed for the above data points.

Once extracted from the EHR, data will be maintained on secure, encrypted, password protected research servers at Mayo Clinic. Access to data files will be restricted to individuals listed in the protocol approved by the Mayo Clinic IRB.

13.2 Data Management

Individual sites in the NOHARM project (specifically MC Rochester, MC Arizona, MC Jacksonville, MC La Crosse, MC Mankato, and MC Eau Claire) will not be required to conduct any site- or study-specific, manual data collection. All study sites use a unified electronic medical record (Epic) and programmatic data extraction can be conducted by study team personnel at the coordinating center (MC Rochester).

The coordinating center (MC Rochester) will extract data from the electronic medical record as needed to assess the fidelity of routine data collection activities, evaluate the completeness of data collection, and to conduct comprehensive data pulls for the final analysis.

Data collection forms are not applicable to our study design as all data will be recorded as part of usual care and electronically retrieved from the medical record by study staff.

13.3 Quality Assurance

13.3.1 Training

Data will be extracted, compiled and analyzed by personnel on the study team who have expertise in data management, informatics and statistical methods.

13.3.2 Quality Control Committee

Data will be electronically extracted from the EHR and validated against the clinical record. Chart-audit will occur at 3-month intervals, on 2-5%, depending on capacity, of patients for each of the most recently activated clusters. These audits are intended to insure that data extraction procedures are functioning as expected for each cluster.

13.3.3 Metrics

The study team will validate electronic data pulls against the EHR as needed.

13.3.4 Protocol Deviations

Protocol deviations will be reported promptly to the Mayo Clinic IRB upon the study team being made aware of the deviations. The main opportunity for protocol deviations is the mis-routing of patients to wrong study arm (intervention or control). Care will be taken to make sure the EHR assignment algorithms are functioning properly. Protocol modifications will be made as new tranches are brought into the intervention arm of the study.

The following are examples of potential protocol deviations which will be carefully avoided, but reported if they occur:

1. Implementing the intervention without practice approvals.

As indicated in the protocol and elsewhere, we will be engaging with practice leadership in advance of implementing the NOHARM intervention. Failure to duly engage practice leadership and obtain documented approval prior to implementing the intervention in specific surgical practices would violate expectations set in the protocol.

2. Incorrect routing of patients to intervention/control arms.

Patient assignment to either the treatment or control arm of the study within the EHR will be done via pre-specified algorithms. Rigorous testing and validation will be done to ensure the algorithms are functioning as expected. Should the algorithms fail to properly assign patients to the treatment or control arm of the study, appropriate action will be taken to refine the algorithms to prevent further mis-assignment and the affected patients will be accounted for, as appropriate, in the study analyses.

3. Failure to monitor trial for data quality and patient safety.

Per the protocol, we will monitor study implementation—particularly within the surgical practices in which the NOHARM intervention has been implemented—to ensure that the intervention is functioning as designed/intended and that critical data points are being captured. Further, the protocol assumes that data essential for monitoring patient safety and ensuring data quality will be abstracted as needed and made available to the data safety and monitoring board for review.

4. Study staff not included in IRB documentation.

All personnel on the study who will be involved with the conduct of the research must be included in IRB documentation per Mayo Clinic policy. This excludes members who are involved with NOHARM as Standard of

Care. Failure to disclose personnel actively involved in the study conduct will constitute a protocol deviation.

5. Failure to apprise the IRB of updated patient contact materials or study procedures.

It is possible that some of the patient contact materials, including elements of the decision aid, after visit summaries, and resource materials provided to patients will be updated with alternate and or additional information throughout the course of the study. Failure to apprise the IRB of these modifications and/or to document these updates as potentially important covariates in analysis will be considered a deviation from protocol.

13.3.5 Monitoring

The study will be monitored by the DSMB in a manner and frequency prescribed by NIA/NIH.

14 PARTICIPANT RIGHTS AND CONFIDENTIALITY

14.1 Institutional Review Board (IRB) Review

This protocol and any subsequent modifications will be reviewed and approved by the Mayo Clinic IRB.

14.2 Informed Consent Forms & Authorization Considerations

A waiver of informed consent is being requested for this study, which presents no more than minimal risk of harm to subjects. Because this is a population-based, EHR-embedded study, it is not practical to conduct the research without the waiver of consent. We do not feel the waiver of informed consent will adversely affect the rights or welfare of the subjects.

In lieu of consent, we have sought out and confirmed Mayo Clinic Practice leadership support for the trial. In the 3-6 months prior to each wave of trial implementation we will confirm each individual practices' willingness to participate in the trial. Because some practices will not be randomized until 2023, securing their endorsement now, did not make sense.

See Section 15 – Ethical Considerations for more information.

14.3 Participant Confidentiality

Information about study subjects will be kept confidential.

Only NOHARM study team members (study investigators, project coordinators, research assistants, data managers, biostatisticians, etc.) who are IRB-approved study staff will have access to individually identifiable private information collected for study purposes, except as necessary for monitoring, audits and/or inspections by the IRB, the NIA, and/or government regulatory agencies.

Data that are transferred outside of the Mayo Clinic firewall will be de-identified, stripped of personal health information, and encrypted.

14.4 Study Discontinuation

The study may be discontinued at any time by the principal investigators, the IRB, the NIA, the DSMB, or other government agencies as part of their duties to ensure that research participants are protected.

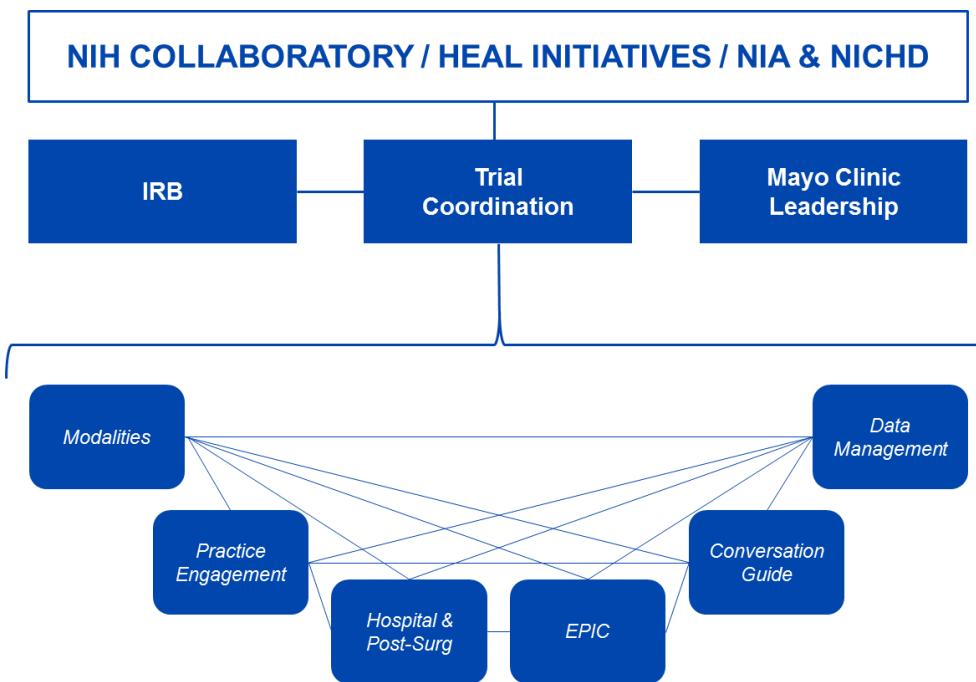
15 ETHICAL CONSIDERATIONS

This is a population-based study, where all eligible patients undergoing qualifying surgeries at participating Mayo Clinic locations will be “enrolled.” 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 Mayo Clinic IRB has been an active partner in developing the NOHARM application and its involvement will continue. Preliminary discussions with the Mayo Clinic IRB executive committee in January 2020 concluded this study is minimal risk and that waiver of consent was warranted so long as practice endorsement was secured.

IRB members and the Mayo Clinic 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 Mayo Clinic Enterprise, in an effort to proactively anticipate ethics, human subject protections, and institutional oversight concerns related to the conduct of quality improvement, pragmatic, and “standard of care” trials convened a group of key stakeholders. These stakeholders include members of the Mayo Clinic IRB, Mayo Clinic 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.

16 COMMITTEES

The following schematic illustrates the Mayo Clinic research team workgroup structure.



16.1 Project Workgroups/Responsibilities

The NOHARM PIs established six workgroups to develop the intervention, engage practice partners, create training material and implement with the surgical practices identified for the trial. Team members meet face-to-face and virtually on weekly/bi-weekly basis and report to the trial coordination team. Meeting notes and progress reports are maintained on a project folder share for team members' reference.

- Trial Coordination
 - Interfaces with the Duke Center, NIH, NIA, and Mayo Clinic IRB, practice leaders and committees.
 - Manages the budget, provides oversight and guidance to the project team.
 - Development and maintenance of study materials including the Manual of Procedures and study forms
 - AE and SAE monitoring and reporting
 - Quality control procedures
 - Distribution of all changes, updates and policies of reports and documents to all participating study sites, NIA and to the DSMB as necessary.

- Modalities
 - Identify scalable NPPC approaches that can be broadly delivered at high fidelity throughout the Enterprise.
 - Develop supportive education material, develop staff training materials, and ensure distribution at target sites.
 - Collaborate with Healing after Surgery Guide and Epic team to develop system content.
- Practice Engagement
 - Characterize peri-operative workflows in the target specialties.
 - Develop and deliver training material.
 - Identify and engage key stakeholders and practice champions.
 - Provide support during implementation
 - Conduct site visits to ensure adherence to the protocol and procedures.
 - Communicates with study sites, responding to and documenting ad hoc communications.
- Hospital / Post-Surgical
 - Develop NPPC discharge plan integration and opioid taper counseling
 - Determine Patient reported outcome assessment and response strategy.
- Epic
 - Define the EHR technical requirements. The EHR components include orders, documentation, best practice alerts, patient questionnaires and reports.
 - Identify and engage technical resources to configure, validate and advance changes through the EHR environments.
 - Obtain approval for the EHR changes from the appropriate committees.
 - Document all components of the EHR build and identify/implement changes required for each tranche implementation.
- Healing after Surgery Guide
 - Conduct interviews, focus groups, and shadowing to gain insights into the user experience from both the healthcare staff and patient perspective to inform the design of the Healing after Surgery guide.
 - Develop and refine the Healing after Surgery guide, collaborating with Mayo Clinic's Office of Patient Education, Integrative Medicine & Health and Department of Physical Medicine and Rehabilitation to define patient educational content.
 - Coordinates the GC build with the Epic MyChart and patient portal teams.

- Data Management
 - Identify clusters based on surgical procedures and sites.
 - Develop the randomization scheme and procedures.
 - Develop the data flow and data management procedures including data entry, error identification and correction.
 - Perform programmatic extraction and curation to support trial analyses as described in section 13.
 - Maintain data security and integrity in concordance with section 13.1 of the IRB protocol.
- Mayo Clinic Leadership

While the NOHARM intervention is designed to seamlessly integrate into clinical practice and hospital workflows, meaningful stakeholder engagement and collaboration is critical to successful implementation. The project team seeks endorsement from Mayo Clinic leaders and practice partners through the established committee structure including:

- Mayo Clinic Clinical Practice Committee
- Opioid Stewardship Program
- Mayo Clinic Nursing Practice Council
- EHR/RMC Oversight Committee
- Surgical and Procedural Committee
- Surgical Specialty Councils

17 PUBLICATION OF RESEARCH FINDINGS

The trial will be registered on ClinicalTrials.gov and the NOHARM investigative team will follow the requirements outlined in the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. Mayo Clinic has an established internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with the policy requirements.

Mayo Clinic strongly supports investigators to present at relevant regional, national, and international meetings. Opportunities such as these are both opportunities to share knowledge and also cultivate new ideas among colleagues. Given our expertise, diverse collaborators, and distinct focus in the project, we foresee a number of manuscript and presentation opportunities. We will publish rigorous visible results in quality journals.

Mayo Clinic's office of Scientific Publications also supports investigators in developing journal articles, chapters, and complete books for academic publication. Additionally, the Mayo Clinic College of Medicine supports the development of educational content throughout its five schools, ensuring that new, groundbreaking ideas are quickly spread to learners at nearly every level of medical education. Importantly, new education spreads beyond our own doors in numerous ways. Especially important is the Mayo School of Continuous Professional Development, accredited by the ACCME.

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19 DESCRIPTION OF SUPPLEMENTS/APPENDICES

19.1 Appendix A: Clinician Participants

Description of the status of clinicians in the NOHARM pragmatic trial.

19.2 Appendix B: Resource List

A brief handout provided to patients before discharge that points them to resources to help them further pursue information on non-pharmacological pain management strategies.

Appendix A: Clinician Participants

Clinician Participants

The clinical practices of care teams involved in the care of surgery patients targeted by the NOHARM intervention—including surgeons, nurses, physical therapists, pain management specialists—will be impacted by the bundled NOHARM intervention. In the course of providing care to surgical patients in active intervention clusters, clinicians will be alerted to non-pharmacological pain management strategies (via CDS tools embedded in the EHR) for which patients have expressed preference. Within their routine workflows (i.e. interface with patients), clinicians will be prompted to engage patients about their preferred post-acute pain management strategies.

Because of this practice impact, clinicians will be considered “participants” in the NOHARM pragmatic trial (in the same way as they have been construed in the pilot application IRB# 20-001864). This determination has been affirmed by the Mayo Clinic IRB executive committee (January 2020 meeting).

Accrual

Based on data from 2018 on the 22 surgery types targeted by the NOHARM trial (minus neuro / spine surgery which is the focus of the NOHARM pilot trial – IRB# 20-001864) we estimate there to be approximately 225 surgeons in the enterprise who are routinely performing surgery. We will inflate this number to 300 to account for physicians performing one of the target surgery types less frequently. To this figure, we will add 0.5 residents / and 0.5 physician assistants per surgeon (+300). Assuming a median hospital stay of 3 days (9 nursing shift changes), we will add 9 nurses X 300 surgeons (+2700). Finally, assuming 0.5 physical therapist per surgeon and 0.2 integrative medicine specialist per surgeon, we will add 210 clinicians. This brings our total estimated clinician accrual to 3510 participants.

Consent and Data Collection

1. Given the ubiquity of the intervention and the volume of clinicians touched by the trial it will not be practicable to obtain individual consent for participation.
2. Clinician “consent” will be granted in the form of “whole practice consent” granted by individual surgical practice leadership within the institution as a pre-requisite for implementation in specific surgical practices.
3. It would be impracticable to formally track clinicians as we are not documenting individual consent nor collecting data from clinicians. Although we could potentially identify the number of clinicians who log into Epic to provide care for discreet surgery patients, this approach would be imprecise.
4. No clinician variables—including clinician ordering or prescribing behaviors—are being assessed. All study outcomes are patient outcomes, as the intervention is intended to guide the patient’s surgical recovery experience.

Risks and Benefits

The risks to clinicians involved in the NOHARM trial are minimal. Clinicians are already motivated to employ clinical guidelines for non-pharmacological pain management, and the NOHARM pilot study may enhance their personal success that effort. Clinicians may find, perhaps at first, that the EHR-based prompts interfere with the rhythms of their workflow, but

great effort has been invested to ensure that the EHR-embedded clinical decision support tools integrate seamlessly into existing workflows. Further, the Mayo Clinic Clinical Practice Committee has endorsed the intervention as an appropriate element for institutional improvement in the management of post-surgical pain. Ongoing care will be taken to minimize the workflow burden while making the EHR prompts an effective tool in promoting institutional adherence to clinical guidelines. Clinicians will always be able to make professional judgments about the appropriateness of engaging patients in specific conversations about pain management throughout the patients' post-surgical recovery. Clinicians may freely disregard EHR-prompts as they deem appropriate in their professional judgment. Clinicians will be amply supported by the study team by way of education and through access to study team members with expertise in non-pharmacological pain management modalities and in the management of complex pain management cases.

Appendix B: Resource List

Patient Support

- Zoom group support calls will help patients by answering questions about the patients' selected modalities. Answers will be provided by NOHARM trial staff. Resources include:
 - [Zoom Group Call Instructions](#)
 - [Welcome Instructions](#)
 - Zoom Group Call Talking Points
- Toll-free number (1-833-919-1432) will help support patients by answering questions about the patients' selected modalities and the NOHARM trial staff will provide answers
- Healing After Surgery Website (www.healingaftersurgery.mayoclinic.org was developed to support patients who are portal users)
- [Healing After Surgery Workbook was developed to support patients, who may not be portal users, may not have access to a computer or to the internet or may not be comfortable with technology](#)
 - [Workbook Cover Letter](#)
- [Transcutaneous Electrical Nerve Stimulation \(TENS\) Patient Education Video](#) is a 5-minute patient education instructional video
- 13 Modality videos. Each video provides a brief modality overview
- [Modality Flyers](#) Each flyer [provides a brief overview of each modality and resource list](#)
- [Rack Card - Healing After Surgery Managing Pain is a quick reference guide \(rack card\) about NOHARM and the NOHARM resources](#)
- [Healing after Surgery DVD](#) includes all patient education video content used in the NOHARM intervention. The DVD mirrors what is on MCTV.
- [Mayo TV NOHARM Resource List provides the NOHARM patient education resources available on Mayo Clinic Television \(MCTV\)](#)
- [NOHARM TENS units: the NOHARM trial will purchase TENS units for the surgical clusters](#)
- [Portal messages](#)
 - Pre-op sending/assignment of Healing after surgery guide: message sent when the patient is assigned the Healing after surgery guide
 - Pre-op Healing after surgery guide non-response reminder message: if the patient hasn't completed the Healing after surgery guide, this reminder is sent.
 - Pre-op post-Healing After Surgery Guide follow-up message/Thank you (4 confidence): 4 messages based on the patient's response to the confidence questions.
 - Post-Op Discharge ("Welcome Home") Message: reminds patients of NOHARM resources after they are discharged from the hospital.
 - 1, 2 and 3 month post-op questionnaire reminder (send 4 days after initial questionnaire was sent): Standard Epic reminder message
 - PROMIS CATs Questionnaire Followup Message: 3 versions depending on the patient's PROMIS CAT scores; reminds patient of NOHARM resources and if their pain and or physical function is severe, then suggest actions the patient should take
 - **Message sent after opioid prescription refill**

Epic Components (Standard of Care)

- - Healing after Surgery Guide is an Epic questionnaire with additional HTML to help patients understand what to expect when recovering from surgery, learn about pain management techniques and to make a plan to manage pain after surgery. There is a [Desktop version](#) and mobile version

- Pre-op questionnaires: Pre-surgery questionnaires are existing PROMIS CAT questionnaires: Pain Interference, Physical Function, Anxiety questionnaires
- 1, 2 and 3 month post-op questionnaires: (Identify intervention patients that need help/struggling; collect data)
- Physical function, Pain Interference, and NPPC usage -and at 3 months a Opioid Usage questionnaire (content complete) along with the PROMIS Anxiety are also given
- [After Visit summary \(AVS\) \(search the folder for AVS to find all files\)](#)
 - Patient facing: Provides patients with information specific to their selected modalities.
 - [Discharge to facility AVS](#): A significant number of NOHARM participants will be dismissed to post-acute care (PAC) facilities, e.g., skilled nursing facilities. For those patients, the AVS content will be directed to clinicians at PAC facilities

Mayo Clinic Care team Support

- Pager (3-5519): NOHARM staff will provide Epic and workflow support
- [Department of Nursing Healing after Surgery \(NOHARM\) Intranet page provides a NOHARM overview as well as available NOHARM resources](#)
- [Provider NOHARM Overview and Talking Points \(elevator speech\) reminds the care team of NOHARM](#)
- MyLearning classes: provide a NOHARM overview, set expectations and teach the NOHARM workflow for each role
 - NOHARM: Introduction and Overview (COURSE 502E00NOHM0001)
 - NOHARM: Provider Training(COURSE 502E00NOHM0004)
 - NOHARM Inpatient Nursing Training (COURSE 502E00NOHM005)
 - NOHARM: Outpatient Nursing Training(COURSE 502E00NOHM0002)
 - NOHARM: Physical Therapy Training (COURSE 502E00NOHM0003)
 - NOHARM: Pre/post-op and PACU Nursing Training (COURSE 502E00NOHM0006)

Epic Components (Standard of Care, support for clinical team)

- [NOHARM Just in Time Training: role based training that is linked in the Epic NOHARM banner](#)
 - [Inpatient nursing](#)
 - [PACU](#)
 - [PT](#)
 - [Surgeons APP resident](#)
- [RN Education points helps RNs provide NOHARM education to patients](#)
- RN Task/Brain/worklist: NOHARM tasks the RN has to complete
- NOHARM Banner: the NOHARM banner is pink to help with awareness
- [RN Orders \(search folder for Orders for all the files\)](#)
- Best Practice Alerts: alert Mayo Clinic care teams about key steps to take for NOHARM. Triggered off of certain Epic event
 - PT/OT BPA
 - Pain > 1 BPA
 - Opioid Rx BPA

Trial Coordination

- [NOHARM Data and Safety Monitoring Board \(DSMB\) Charter](#)
- [NOHARM Data and Safety Monitoring Plan \(DSMP\)](#)
- [Letters of Support](#)

