Study Title:

Motivational Interviewing and Guided Opioid Tapering Support to Promote Postoperative Opioid Cessation

NCT03659734

Document Date: 10/15/2020

MAP-Pain Standard Operating Procedures

Study Overview

Name of study: Mood and Postoperative Pain (MAP-Pain) Trial

Enrollment Goals:

Observational Arm N = 558*

Intervention Arm N = 220*

*Assumes 15% attrition in the observational arm, and 10% censoring in the intervention arm

Start Date:

IRB approved April 18, 2018

NIH Certificate of Confidentiality: Automatically granted for NIH-funded research.

Patient Endpoint Definition:

Observational Arm: The endpoint is the first of 2 consecutive reports of zero overall opioid use. Secondary endpoint is opioid misuse defined as a score of 9 or higher on the Current Opioid Misuse Measure. In addition to the endpoints defined above, time to pain cessation (1st of 2 consecutive reports of zero average pain) and indicating they consider themselves recovered from surgery are additional endpoints.

Intervention Arm: The endpoint is the first of 2 consecutive reports of return to baseline opioid dose or lower. Secondary endpoints are opioid misuse defined as a score of 9 or higher on the Current Opioid Misuse Measure, and time to complete opioid cessation (1st of 2 consecutive reports of opioid cessation).

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Education and Training

Research Staff

All research team members will perform the responsibilities as outlined by the delegation of authority log. Human Subjects Training, CITI training, and HIPAA training will occur as required by Stanford Policy. Additionally, all team members will receive a copy of this document, the Lab Policy Manual, and will be trained directly by the Principal Investigator (PI) or Lead Clinical Research Coordinator (LCRC) on the purpose of the study and their responsibilities. Research staff will be trained on Informed Consent, Phone Screening, and Case Report Form Completion by the research manager, who will monitor appropriate conduct and form completion on an ongoing basis, in collaboration with the PI and study monitor. Recruitment and patient contact will first be conducted under the direct supervision of the PI or LCRC, until they deem the research team member capable of carrying on responsibilities independently. Research team meetings will occur frequently with the PI to ensure ongoing understanding by study staff and to address any concerns.

Training for the Intervention Arm

Training of the NP (Tracey Mallick) will be supervised by S. Berg-Smith, and include a 3-day introductory intensive workshop introducing the theory, principles, and skills of MI and related motivation-enhancing, behavior change approaches; and a 3-day advanced training workshop. Learning activities will include demonstrations, video examples, “real-plays”, case studies, and small group exercises. Pilot MI+GOW sessions completed by T. Mallick will be evaluated using global ratings from the MI Treatment Integrity coding system 4.0. Prior to counseling study participants, ratings ≥3 on all global scores (cultivating change talk, softening sustain talk, partnership, and empathy) of 2 consecutive pilot participants will be required. Ongoing supervision of MI skills will include monthly reviews of recorded interventions (after MI treatment integrity coding) and meetings with S. Berg-Smith to optimize treatment fidelity and minimize drift.

The Principal Investigator (PI), Dr. Jennifer Hah, will train the NP (Maristella Butler) on the components of the enhanced usual care calls including topics of: 1) standardized instructions on taking opioid medications after surgery, 2) safe opioid use, 3) avoiding medication mistakes, 4) local mental health resources (including a suicide prevention hotline), 5) alternative methods for pain management after orthopedic surgery, 6) understanding complementary and alternative medicine, and 7) prescription drug abuse.

Principal Investigator

The Principal Investigator, Dr. Jennifer Hah, will speak directly with all participating surgeons and preoperative clinic staff to inform them of the purpose of the research and the process for recruitment and patient referrals. Referring physicians will be informed of the study design such that they are aware of what intervention their patients may be receiving. A Q&A form will also be provided to the patient’s physician(s) for informational purposes.

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Recruitment

Recruitment may take place via one of following methods:

Clinical staff referral

Surgeons, anesthesiologists, or clinical care staff may ask a patient if they are interested in speaking with a member of the research team. With the patient's permission, the staff will fill out an "okay to contact" form that indicates permission by the patient for a member of the research team to contact them about research studies that they may be interested in. This form will be submitted to and stored by a Surgical Coordinator, and be collected by a study team member weekly. A member of the research team will document OK to contact forms, and input participants into the REDCap MAP-Pain Enrollment project for screening and enrollment.

Direct Contact

Clinical staff may also inform research staff of those who can be approached directly. Direct approach with prior permission from providing staff may take place in the Anesthesia Preoperative Evaluation Clinic, or the orthopedic clinic, or via the clinic schedulers. The research coordinator should ask the patient if he/she is interested in participating in a postoperative pain research study and fill out the "okay to contact" form accordingly. The patient should be consented at a later time.

CT.gov posting

The STOP clinical trial is posted on the Stanford Clinical Trial site, which is uploaded to clinicaltrials.gov. Site status is listed as "enrolling by invitation". Interested patients may contact the study team at the contact information provided, but will only be considered for inclusion if they are receiving an eligible surgery at Stanford Hospital and Clinics.

Perioperative CHOIR

Patients completing Perioperative CHOIR as part of their routine care prior to, or during their visit to the Anesthesia Preoperative Evaluation Clinic may elect to enroll in the study directly, and complete additional questions after information regarding the study is provided. Patients will be contacted at a later date by the research team to obtain written informed consent for continued participation in the study.

Email Invitation Survey

Patients scheduled with the Anesthesia Preoperative Evaluation Clinic are automatically screened, and patients meeting basic inclusion criteria are identified. Identified patients will be contacted via invitation email, and invited to complete a brief online screen to determine eligibility and interest. All eligible potential participants will be contacted by the research coordinator by phone. The coordinator will call the patient three times or until the patient picks up. If possible and necessary, the coordinator should leave a voicemail and specify the first name of the patient, give a quick summary of the study, and leave a return name and number. Patients will first be given a description of the study as per the approved phone screen to assess interest and answer any questions (see *Screening Questions* document).

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Phone Invitation Survey

Patients scheduled with the Anesthesia Preoperative Evaluation Clinic are automatically screened, and THR/TKR patients meeting basic inclusion criteria are identified. If participants are unable to be contacted via email, the research team will call to determine eligibility and interest. The coordinator will call the patient three times or until the patient picks up. If possible and necessary, the coordinator should leave a voicemail and specify the first name of the patient, give a quick summary of the study, and leave a return name and number. Patients will first be given a description of the study as per the approved phone screen to assess interest and answer any questions (see *Screening Questions* document).

Screening

Inclusion criteria

1. Age 18 and above, inclusive†
2. Scheduled to undergo elective surgery at Stanford Hospital†
3. English speaking
4. Ability and willingness to complete assessments via the internet†
5. Scheduled to undergo total knee replacement or total hip replacement at Stanford Hospital*

Exclusion Criteria

1. Inability to complete assessments, (education, cognitive ability, mental status, medical status)
2. Pregnant women†
3. Elevated suicidality as assessed by an answer of 2 or greater on question 9 of the Beck Depression Inventory*
4. Current pain management provider*
5. Enrollment in another perioperative trial*

*Applies to Intervention Arm only
†Assessed via Email Invitation Survey

To attain a more comprehensive understanding of the patient's medication, the research coordinator may need to access the electronic health record (EPIC). EPIC can be used to confirm a patient's medications during the phone screen.

Observation Arm

For the observation arm, patients undergoing any eligible elective surgery at Stanford will be considered for inclusion *(See MAP-Pain Observation Eligible Procedures)*.

Patients will be recruited via methods described above. After completion of the phone or email eligibility screening, the research coordinator will contact all participants to obtain full electronic consent for continued study participation.

Intervention Arm

For the intervention arm, the following operations will be considered for inclusion. These are chosen for the appropriateness of the intervention in the context of the surgery, and the willingness of the surgeon to refer eligible patients.

Total Knee Replacement

Total Hip Replacement

Patients will be recruited via methods described above. Initial screening will take place via a brief online eligibility survey, or with an approved phone screen either on the phone or via an in-person interview during the patient's pre-operative appointment. Patients will first be given a description of the study as per the approved phone screen to assess interest and answer any questions (see *Screening Questions* document). Eligibility will be determined by the research coordinator and/or PI, who will input responses to screening questions into REDCap or complete an eligibility checklist at the time of screening (see *Eligibility Checklist* document). Eligibility to continue into the intervention randomization will be confirmed at 2-weeks post-surgery. Patients who do not meet the criteria at this time-point will continue in the observational arm.

Patient Eligibility and Enrollment

Eligible and interested patients:

Priority consent is the Intervention; observational consent is offered secondarily when a patient is ineligible or not interested in the Intervention.

Written Informed consent may be obtained electronically, through completing of the "Electronic Consent" instrument through REDCap.

Live phone consent - For eligible and interested patients who have a working device that has access to the internet at the time of the consent, a url-link to the electronic consent form should be sent to the participant through REDCap. The research coordinator will select the appropriate consent type (Observation or Intervention) via radio button, check the "Send Consent Form" box, and save the REDCap instrument to email the participant the link. If the participant has not received the email link after five minutes, the Coordinator will manually compose a survey invitation email, and send it to the participant. Participants should be alerted that the research coordinator will read through the consent form with them, taking a maximum of 20 minutes to complete the process. The participant should only sign the form once all his/her questions have

been answered. Completion of the Electronic Consent Form will be verified by the research coordinator, who will view the form upon submission.

Later-date phone consent – For eligible and interested participants who do not have live access to a device with available internet or for those who do not have time to go over the consent form with the research coordinator at the time of the call, a url-link to the electronic consent form may be sent to the participant through REDCap. The research coordinator will select the appropriate consent type (Observation or Intervention) via radio button, check the "Send Consent Form" box, and save the REDCap instrument to email the participant the link. Participants should be told to contact the research coordinator with any questions they have regarding the form *before* they sign it. During the call, the research coordinator may highlight the participant responsibilities, as listed on the consent form, and emphasize study procedures and confidentiality. Completion of the Electronic Consent Form will be verified by the research coordinator, who will view the form upon submission.

Once completed, signed consent forms will be stored in the File Repository of the MAP-Pain Enrollment REDCap Project.

Patients not interested or ineligible:

Patients who are ineligible or not interested in proceeding with the intervention will be offered enrollment in an observational only arm in which no intervention is given, but participants complete the same baseline preoperative questions, and are followed longitudinally with the same questionnaires. Informed consent for the observational only arm will proceed in the same manner as the full trial using the appropriate, approved consent form (see *Observational Trial Consent with COC* document). Consent is obtained via one of the same three methods mentioned for intervention trial consent.

Patients who are not interested in the clinical trial component or the observational component or unable to participate in either arm due to eligibility concerns will be asked to provide basic de-identified demographic information to allow comparison with participating patients using the Anonymous Data Form (see *Consent for Anonymous Data* document). This may be obtained through discussion with the patient him/herself or by accessing the patient's medical record. Patients should be asked the reason they chose not to participate.

Patient Rewards

Patients enrolling in either the trial or observational arms of the study are rewarded at three time-points:

- $20 Amazon EGift Card for completing the baseline questions
- $20 Amazon EGift Card for completing the 6-month follow-up assessment
- $20 Amazon EGift Card for completing the 12-month follow-up assessment

Rewards will be distributed automatically from a group of available gift cards stored in the "MAP-Pain Rewards" REDCap Project upon completion of relevant assessments. Alternatively, rewards will be distributed individually by the study staff upon completion of relevant assessments.

EGift Cards will be obtained through the Administrative Assistant (Kristen Honesto) as needed. The study team will complete and sign a *Human Subjects Incentive Compensation Form (HSIC)* for all participants receiving rewards upon exhaustion of available gift card codes.

Participant Copy of Consent Form & Patient Welcome Packet

Upon completing consent, all participants will be sent a standard welcome email with study team contact information, a copy of their signed consent form, and the Bay Area Resources brochure.

Participant Initiation

Immediately after receiving (and if applicable, locking the consent form), the date of consent must be filled in COORD: Consent Call. The Baseline Questionnaire must be sent via REDCap by checking the correct box. Participants are encouraged to complete the Baseline Packet immediately. The research coordinator will schedule the Pre-Surgery for the first workday preceding their date of surgery, and confirm the pre-surgery call appointment with the participant. The coordinator will save the form to send the Baseline Packet URL-Link to the Participant, and schedule the pre-surgery call in the REDCap Calendar.

Pre-Surgical Assessment

Baseline Questionnaire Packet

After enrollment, participants will complete a pre-surgical questionnaire packet (AKA the Baseline Packet) via REDCap. Participants are given access to the Baseline Packet immediately after Electronic Consent is obtained and reviewed, and are encouraged to complete it immediately after receiving access.

Pre-surgical assessments in addition to Preoperative CHOIR are documented below:

1. Contact, surgical, and demographic information (labeled "Baseline Packet" in REDCap)
2. PHQ-9 – Patient Health Questionnaire-9
3. Baseline BPI-II – Modified Brief Pain Inventory-II including PAINMAP.
4. BPOQ - Baseline Pain and Opioid Questionnaire (Current opioid use and addiction susceptibility)
5. HADS – Hospital Anxiety and Depression Scale
6. TAPS - Tobacco, Alcohol, Prescription medications, and other Substance Tool
7. COMM – Current Opioid Misuse Measure
8. DSO - DSM-5 Opioids
    a. Administered if COMM Total Score >9
9. BDI – Beck Depression Inventory-II

10. ACE- Adverse Childhood Event Questionnaire
    a. Administered to Observation Participants only.
11. PROMIS Measures
    a. PROMIS Bank v1.0- Depression
    b. PROMIS Bank v1.0- Anxiety
    c. PROMIS Bank v1.0- Sleep Disturbance
    d. PROMIS Bank v2.0- Physical Function

Pre-Surgical Call Scheduling

Once consent is obtained, the research coordinator will schedule the Pre-Surgery Call with the participant. This call is to be scheduled the first workday prior to the participant's date of surgery. Unless a specific timeslot is requested by the participant, Pre-Surgery calls should be scheduled at 23:15 in the REDCap Calendar, and completed in the afternoon.

Pre-Surgical Call

The research coordinator should call the participant on the first workday prior to the date of surgery. During this call, the coordinator should confirm completion of the Baseline Packet and reception of the gift card code reward. The coordinator will confirm that the participant has a time slot scheduled on their date of surgery, and schedule the post-surgery follow-up call fourteen days after the participant's date of surgery. The coordinator will remind the participant that online follow-up assessments will commence once week after surgery.

If this call cannot be completed, the research coordinator should leave a voicemail message reminding the participant of participation in the study, and describing upcoming follow-up dates (week 1 assessment, post-surgery follow-up call). This message should include contact information for the coordinator, and instructions to contact the research team if the surgery has been cancelled or postponed.

Transfer to Longitudinal Study

On Monday and Friday of each week, participants who have completed all pre-surgical assessments and are past their date of surgery will be transferred to the MAP-Pain Longitudinal Observation REDCap project for follow-up. Participants to this transfer are identified by the "Move to Longitudinal" REDCap Report (Report ID# 58489). Each Monday and Friday, the report will be edited to include only participants completing their surgery on or before the day of transfer, and after the date of the last transfer.

Participants meeting transfer criteria will be assigned a new longitudinal record ID through the "Info Transfer to Operations" Instrument in the Enrollment REDCap project. The Record ID is to be formatted as First Initial Last Initial-Record ID in enrollment Project (displayed as AA-0000). The Surgery type is to be selected. Observational Participants (non-THA/TKA procedures) are to be recorded in the "Other Surgery Type" text field, "mark the form as "complete", and save the form to complete the transfer.

For intervention Participants (THA/TKA procedures), mark the form as “unverified”, and save the form to complete the transfer. The form is not to be marked as “complete” for intervention participants until post-surgical follow-up is completed, and the participant has been randomized or assigned to the observational study.

Post-Surgical Assessment

Post-Surgical Call Scheduling

During the pre-surgery call, the coordinator will schedule the post-surgical call fourteen days after the participant’s date of surgery. Unless a specific timeslot is requested by the participant, Post-Surgery calls should be scheduled in the REDCap Calendar at 23:45 for observation participants, and 23:59 for intervention Participants.

Post-Surgical Call

Fourteen days after the participant’s date of surgery, the study coordinator will call the participant to confirm their date of surgery, the date and time they were discharged from the hospital, and verify if the participant has been prescribed and is still using opioid medications for surgical pain. The coordinator will call the patient five times, or until the patient picks up. If possible and necessary, the coordinator should leave a voicemail and specify the name of the patient, the purpose of the call, and leave a return name and number. If appropriate, the coordinator will randomize the study participant immediately after their call.

Randomization

During the Post-Surgical Call (Fourteen days after surgery) the research coordinator should verify whether or not the intervention participant in question has been prescribed and is still using opioid medications for surgical pain. Those who meet this criteria will be randomized to either the Motivational Interviewing and Guided Opioid Weaning intervention, or Enhanced Usual Care. Those who do not meet this criteria will be placed in the Observational arm of the study.

Participants are randomized in the Transfer to Longitudinal Instrument in the MAP-Pain Enrollment REDCap. Upon clicking the “Randomize” button, the coordinator will be prompted to select the surgery type (THR/TKR) and confirm the randomization. The participant will be randomized to “1” or “0”, denoting MI+GOW and EUC respectively. Once randomized, the part the participant cannot be moved to a different study group, so care must be taken to ensure participant is randomized correctly.

After random group assignment, the Transfer to Longitudinal instrument must be saved to transfer the participant's group assignment to the MAP-Pain: Longitudinal Observation REDCap project. The coordinator will send an email to the appropriate NP, to inform them of a newly randomized participant, and set up an appointment for MI+GOW or EUC sessions to begin.

Blinding and Randomization Methodology

Randomization table was pre-generated using SAS. Randomization occurs using blocked, stratified randomization by operation. Randomization table was pre-generated onto spreadsheets, with rows hidden (in Excel). Each randomized patient will receive the next available row (unhidden by the coordinator at 14 days post-surgery for randomization as needed).

The PI will be blind to the patient's randomization status until completion of analyses. Due to the limitations of REDCap's randomization module, the research coordinator cannot be blinded to the randomization status of the participant.

Enhanced Usual Care (EUC)

Participants will receive phone calls matching the duration and frequency of MI+GOW calls. Maristella Butler, NP will contact participants via phone to review one topic per call in this sequence: 1) standardized instructions on taking opioid medications after surgery, 2) avoiding medication mistakes, 3) alternative methods for pain management after orthopedic surgery, 4) understanding complementary and alternative medicine, 5) safe opioid use, 6) local mental health resources (including a suicide prevention hotline), 7) prescription drug abuse. She will briefly review patient education brochures in a didactic style without a tailored discussion. She will remind participants to complete REDCap assessments.

Intervention

The experimental intervention arm is Motivational Interviewing and Guided Opioid Weaning (MI+GOW). A pain medicine nurse practitioner (Theresa Mallick-Searle, NP) will administer MI+GOW. See table below for MI Components. The GOW protocol will be a 25% total daily opioid dose reduction every 7 days with opioid discontinuation 7 days after reaching 1 opioid pill per day. During phone sessions, patients will be monitored for worsening pain and opioid withdrawal through administration of the NRS and SOWS with the protocol specified in the "Guided Opioid Weaning" table below. Participants will be reminded that they can always use less opioids than recommended. Non-adherence is opioid use greater than previously recommended via the last phone call. During the randomization call, the first MI appointment should be scheduled by referring to Tracy Mallick's schedule.

Table MI Components

Principles	Strategies	Information Recorded by Interventionist	Information and Advice Offered in an MI-consistent manner (Elicit patient's knowledge, Provide advice, Elicit feedback)

Engaging and focusing the agenda	● Thank for participation ● Share the agenda and discuss autonomy ● Answer patient questions	● Preferred contact phone number and times for calls	● Explain the role of the interventionist and discuss length of phone calls
Enhance motivation to wean opioids	Elicit self-motivational statements that support the following: ● The patient's recognition of opioid side effects and the risks of opioid misuse, addiction, and overdose ● The patient's concern about how he or she is currently managing their pain medications ● The patient's own reasons to stop opioid use ● The patient's intention to wean or stop taking their opioids. ● The patient's optimism that opioid cessation is possible. ● Identify personal strengths and goals	● Current pain management including non-opioid medications and adjuvant treatments (e.g. icing, acupuncture) ● Opioid-related adverse effects ● Patient's reasons for opioid weaning/cessation	● Informing patients of current opioid and non-opioid prescriptions prescribed by the surgeon ● Education regarding multimodal postoperative pain management ● Information regarding opioid-related adverse effects patient is experiencing (e.g. management of opioid-induced constipation)
Strengthen commitment to opioid weaning	● Help the patient develop a plan for weaning ● Communicating free choice ● Review consequences of continued opioid use vs. cessation ● Explore barriers to opioid weaning and identify support ● Elicit a final commitment	● Current NRS score ● Current SOWS score ● GOW recommendations for the following week ● Patient's plans for tapering opioids and optimizing pain management ● Contingency planning for barriers	● Advice concordant with GOW protocol based on NRS and SOWS scores ● Information regarding optimal timing of pain medication doses for maximal effect ● Information regarding current opioid tapering guidelines
Relapse prevention (non-adherence to the GOW protocol)	● Reviewing progress: Any progress should be praised and reinforced as much as possible ● Renewing motivation: Review behavioral indicators of motivation, and patient's responses to questions for reasons for weaning or continuing to taper opioids ● Renewing commitment: ○ Discuss what can be learned from non-adherence ○ Revise the opioid weaning recommendations and obtain a commitment to follow-through with the revised plan	● Episodes of non-adherence to GOW protocol, and reasons for non-adherence ● Perceived barriers to opioid weaning (e.g. physical therapy causing increased pain)	● Education regarding safe opioid storage and disposal. ● Education regarding opioid misuse. ● Advice to increase self-efficacy (e.g. encouraging patient communication with the surgical team and efforts to increase physical activity)

Key MI Tools for GOW Sessions

- **Open-ended questions to evoke patient's goals for pain management and opioid cessation**
- **Affirmations to focus on strengths, abilities, or efforts to reduce opioid use**
- **Reflective (empathic) listening, strategically emphasizing "change talk" such as patient-generated reasons to wean opioids**
- **Summarizing "change talk" focusing on desire, ability, and reasons for opioid weaning**
- **Developing discrepancies between goals for opioid cessation and current behavior**
- **Avoiding argumentation for opioid tapering**
- **Handling resistance, through reframing or reflecting patient's views to elicit patient's arguments for opioid cessation**
- **Supporting self-efficacy, noting effort to taper opioids to foster patient's own belief in their ability to reach opioid cessation**

Guided Opioid Weaning Protocol

Mean SOWS Score	NRS Score	Total Daily Opioid Dose
> 2	> 7	25% Increase
≤ 2	≤ 7	25% Decrease

> 2	≤ 7	Maintain Current Dose
≤ 2	> 7	25% Increase

Schedule

Both groups will receive weekly phone calls from weeks 2 to 7, and at week 11 for 7 total calls. All calls will be limited to 20 minutes, and the duration of each call will be recorded.

Rescheduling of the intervention can occur up to 31 days after the previous session; if patient is unable to receive the intervention within this timeframe, the patient will be moved to observation-only follow-up.

The first session will be scheduled by the research coordinator; subsequent appointments will be made directly between the NP's and the patient. The first session must be scheduled between 14 and 21 days after the participant's date of surgery. After the initial call, NP's will be responsible for tracking and competing intervention calls.

Intervention Protocol

Participants randomized to MI+GOW will receive the intervention from a single provider (T. Mallick). Of note, participants will have all opioids and additional pain medications prescribed by their surgeon during the study. T. Mallick will only be providing advice regarding participants' opioid medications. Content of the MI call is detailed in the Intervention section above. Treatment engagement is defined as participation in >50% of phone sessions. Treatment initiation is defined as participation in at least 1 phone session.

Longitudinal Follow-up

Scheduling Follow-Up Assessments

Electronic surveys will be sent out automatically based on confirmed dates of surgery. Distribution of online assessments will occur via the REDCap survey invitations calendar defined in the Longitudinal Observation Project, beginning seven days after the date of surgery. A patient's official date of surgery will be entered into the "Pre-Surgery Call" instrument in REDCap during the Pre-Surgery call, and confirmed during the Post-Surgery call. The study team member may verify the date of surgery and time of discharge in EPIC and record it on the "Post-Surgery Call" instrument.

Medical Chart Review

Research team member will review the patient's medical record for information required on the case report form.

Compliance Monitoring

Participant compliance with follow-up assessments will be assessed weekly through an automated reporting dashboard. Patients failing to complete two consecutive follow-up assessments be contacted

by the research coordinator, to encourage continued participation. The coordinator may offer to limit the participant's follow-up to monthly surveys, to maintain follow-up data collection for the participant.

Survey Frequency Reduction

To reduce instances of participants lost to follow-up or withdrawing, the coordinator can reduce the frequency of participant surveys from weekly to monthly. To complete this, the coordinator will check the "Monthly Surveys Only" checkbox in the "Coordinator Controls" instrument of the Longitudinal Observation REDCap project, and save the instrument.

Lost to Follow-up Participants

A participant is considered "Lost to Follow-up" if they have not completed a follow-up assessment for two months, and cannot be reached by the research coordinator. The Research coordinator will attempt to call the participant three times before declaring them lost to follow-up, leaving a voicemail message able. If a participant has alternative numbers listed (like a spouse or relative), those numbers should be attempted many times before inactivating the participant.

If the coordinator has determine the participant is lost to follow-up, the coordinator will mark the participant status as "Inactive" in the Coordinator Controls Instrument of Longitudinal Observation REDCap. The coordinator will also input the date of last contact with the participant, and select "Lost to follow-up" as the reason for withdrawal. Participant notes may be used to elaborate on the circumstances of the participant's withdrawal.

Patient Withdrawn or Study Completion

If a patient is withdrawn from the study, the study coordinator will mark the participant status as "Inactive" in the Coordinator Controls Instrument of Longitudinal Observation REDCap and document the date of the last contact and reason for withdrawal. The study coordinator will also input the date of last contact with the participant, and select "Lost to follow-up" as the reason for withdrawal. Participant notes may be used to elaborate on the circumstances of the participant's withdrawal.

Weekly and Monthly Surveys

Weekly Assessments

The following assessments will be completed weekly via online assessment up to 6 months, and then monthly up to 12 months for all participants.

1. Weekly Pain and Opioid Questionnaire (WPOQ, combined into one instrument with BPI)
2. Modified Brief Pain Inventory-II (BPI, combined with WPOQ into one instrument)

Monthly Assessments up to 6 months

The following assessments will be completed monthly via online assessment up to 12 months for all participants.

1. Patient Health Questionnaire-9 (PHQ-9)

2. Common Opioid Misuse Measure (COMM)
3. PROMIS Measures
    a. PROMIS Bank v1.0- Depression
    b. PROMIS Bank v1.0- Anxiety
    c. PROMIS Bank v1.0- Sleep Disturbance
    d. PROMIS Bank v2.0- Physical Function

Monthly Assessments from 6 to 12 months

From 6 to 12 months, online assessments alternate to reduce participant burden. These assessments can be grouped in to the following categories

Regular Monthly Assessments

Administered via online survey monthly. Assessments Include:

1. Common Opioid Misuse Measure (COMM)
2. PROMIS Measures
    a. PROMIS Bank v1.0- Sleep Disturbance
    b. PROMIS Bank v2.0- Physical Function

Alternating Monthly Assessments

These assessments alternate each month, the help reduce participant burden. Assessments Include:

1. Patient Health Questionnaire-9 (PHQ-9): Assessed on Weeks 24, 32, 40, and 48
2. PROMIS Measures: Assessed on Weeks 28, 36, 44, and 52.
    a. PROMIS Bank v1.0- Depression
    b. PROMIS Bank v1.0- Anxiety

Irregular Assessments

The following assessments are to be completed via online assessment at time points in addition to Weekly/Monthly Assessments, or have schedules that are best described more specifically.

1. Self-Efficacy for Appropriate Medication Use Scale (SEAMS): Administered to intervention participants on Week 1 only
2. Motivation Interviewing Rulers (MI-Rulers): Administered to intervention participants on Weeks 2, 4, 7, and 12 only

Censoring

Participants may be withdrawn for the following reasons:

- Additional surgery
- Postoperative complication
- Death

- Patients expressing concerns regarding pain management will be offered study withdrawal and referral to a pain medicine specialist

Withdrawn participants will be removed from all future data collection.

Patient Withdrawn or Study Completion

If a patient is withdrawn from the study, or lost to follow-up, the study coordinator will document the events by filling out the "Study Stop Point" instrument electronically in REDCap.

Upon a patient being withdrawn or lost to follow-up, the study coordinator must also go into the REDCap instrument "Participant Entry" and switch the patient's status to "Inactive." At that point a warning message will automatically appear listing all of the future events for that participant, which the coordinator will then remove by clicking "Clean up Calendar Entries" under the project bookmark heading on the left side of the screen. Coordinator will also clean up calendar entries in the Calling Project for participants who have withdrawn or reached study completion.

Data Management

Data will be maintained on appropriate case report forms and participant questionnaires. Case Report Form data will be entered into a REDCap database.

Patient Identification Codes

Both Intervention and Observation arm participants will receive two unique codes identifying their records, saved as the "record_id" in both projects. In the Enrollment project, this code is a 4-digit number, assigned sequentially and automatically when the participant's information is imported into the project (Example: 0000). In the Longitudinal observation project, the research coordinator assigns an alphanumeric code to serve as the participant's record_id, consisting of their First and Last Initial, and the enrollment record_id (Example: AA-0000)

Tracking Events

Consent, Pre-Surgery, and Post-Surgery calls will be tracked in the REDCap Study Calendar, and are generated by completion of the brief eligibility screen, and manual scheduling by the research coordinator.

Online assessments will be distributed and tracked by the Longitudinal Event Calendar in the Longitudinal Observation REDCap Projects

Intervention calls are initially scheduled between the research coordinator, participant, and appropriate study team member. All subsequent calls will be independently scheduled and tracked by the NP and participant.

Hard-copy Data Storage

All data received or collected in paper form must filed in lockable cabinets, and documented in the appropriate event of the REDCap Enrollment Project. Physical Okay to contact forms, Eligibility checklists, screening checklists, and consent forms must be filed in a binder and stored in lockable cabinets.

Okay to Contact Forms

Nurse practitioners or physician assistants in the Ortho-Joint located at 450 Broadway St. Redwood City, CA will ask their patients during their preoperative visits if they would like to be contacted about a pain study. These forms, known as "okay to contact" forms, should be picked up at the ortho-joint clinic weekly. When the status of a participant is determined, the okay to contact forms should be placed in the appropriately labeled binder (one binder per study calendar year) and locked. The coordinator will review the patient's EPIC health record to collect the necessary information to create a REDCap record for the participant.

Screening & Eligibility Forms

Screening information will be maintained electronically in the REDCap enrollment project, in the "Initial Eligibility Survey" instrument or "COORD: Consent Call' instrument. Screening information will be complied regularly into a report detailing the patient name, the date the screening occurred, the method of screening, the study team member performing the screen (if applicable), the screening result (eligible, ineligible, declined to participate and reason), whether the patient was enrolled, and any comments.

Consent Forms

Electronic Consent forms will be stored in PDF format in the File Repository of the REDCap MAP-Pain Enrollment Project. Hard copy consent forms should be scanned and uploaded to the REDCap File Repository as backup storage. Physical Copies of consent forms will be stored in a study binder in a secure cabinet.

For every consent form that is signed, regardless of method of signing, a copy of the signed form must be sent to the participant. For those signing online, a *secure* email (sent by writing "Secure:" in the subject line) with the signed consent attached must be sent. For those signing in paper form, a hard copy of the signed form must be sent via mail.

For Intervention participants, a copy of the consent form will also be sent to Medical Records for storage in the patient's chart; this will have the patient's MRN on each page. The electronic consent document from REDCap will be printed out and will include an electronic version of the study bar code, or a sticker with the study bar code. It is then sent to HIMS, room HC032, MC5200, with coordinator's contact information included. If asked, MAP-Pain has been IRB approved to use the eConsent method; participant names typed into the eConsent form are in lieu of signatures.

Patient Adherence

Non-adherence is considered greater than recommended opioid use that is still within the range of the patient's prescription.

Patient Retention

Patient retention is at its highest rate when participants feel like they are aware of what is occurring in the study, when they have their needs met, and when they are greeted with optimistic and attentive staff.

To keep participants engaged:

- Research staff must ensure that participants know exactly what the study goals are and how the study staff are working to meet these goals.
- Participants should be completely aware of what is required for effective, active participation. The level of time commitment must be made clear at the beginning in order to avoid future dissatisfaction.
- Participants should know that we greatly appreciate their efforts, especially since they are volunteering their time. It must be made clear how important their contribution is to this science.
- Participants must be told that they can withdraw from the study at any time even though we would be sad to let them go. They must be made aware of the effort it takes on all fronts in designing this study and collecting data, so they should try their best to remain in the study.
- Research staff must ensure that all other staff know what to communicate to participants, especially in times of dissatisfaction.

To retain participants who are dissatisfied with the study:

- If the issue comes from participants feeling overwhelmed by assessments, research staff must make an effort to reduce assessments. (See *Survey Frequency Reduction* above)

Trial Safety

Potential Risks & Response to Risks

Risk of Telephone Contact

The primary risk of telephone and online contact involves breach of confidentiality. All research personnel are trained in confidentiality procedures and adequate protections will be in place to minimize this risk. All research personnel must be HIPAA trained. Personnel enrolling participants must complete CITI training.

Risks of Intervention

In addition to risks of confidentiality, there are few other risks involved in enrollment into the intervention. Those who are randomized into MI+GOW may be exposed to greater risk. These risks, however, are only relevant if a participant follows the recommendations. Because T. Mallick is not a part of a participant's regular care team, the participant has the freedom to choose which recommendations to follow, with no obligation to follow any at all. T. Mallick's role is to recommend courses of action that meet the participant's needs, to the extent that it does not do additional medical harm.

Despite these rules, the following are risks that may be associated with participating in MI.

The physical and psychological risks to subjects are the effects opioid withdrawal including tachycardia, diaphoresis, restlessness, rhinorrhea, bone or joint aches, gastrointestinal upset, tremor, irritability, anxiety, and piloerection. Also, patients may experience increased pain if opioids are tapered prematurely. The seriousness of these side effects is moderate, as withdrawal symptoms and pain will be monitored during the intervention. Protocols are in place to hold the tapering schedule with the development of moderate opioid withdrawal and to increase the opioid dose with the development of severe pain. This type of opioid withdrawal is not fatal (as opposed to iatrogenic opioid withdrawal precipitated by opioid antagonists that could lead to mortality). Patients will be encouraged to contact the nurse practitioner (T. Mallick) at any time regarding the development of any adverse effects. Patients will be able to reach the PI (Dr. Hah) or an alternate qualified member of the research team 24 hours a day. Also, participants reporting dramatically increased pain potentially related to other medical causes-e.g. infection, dislocation, thromboembolic disease, new neurologic deficits, will be referred to their nearest emergency department, and their PCP or surgeon will be contacted at the discretion of T. Mallick or Dr. Hah.

The alternative treatment is enhanced usual care, and a subset of these participants is at risk for delayed opioid cessation and potential opioid misuse and abuse. Although participants will be instructed to call 911, or to seek immediate medical attention for medical emergencies, we will encourage participants to call regarding any questions or unusual symptoms they are experiencing. Also, participants will be instructed to contact their primary care provider or surgeon for medical questions unrelated to the study.

Trial Stopping Rules

Given that the research does not involve a high-risk intervention or a population based on previous studies, absolute stopping rules will not be identified in the statistical plan. Any individual participant may choose to end participation for any reason, and this will be noted. The PI may choose to end an individual participant's participation if the participant is non-compliant with study procedures such that the study integrity is harmed or the participant is put at risk by continued participation.

Reporting Study Events to the IRB

Adverse Event Reporting

An adverse event is defined as any undesirable symptom or event experienced by the participant while he/she is in the study. An adverse event can be expected, unexpected, related, or unrelated to the study. If the event does not require great intervention and is addressed by the participant's normal care team, it can be recorded as a study adverse event and does not have to be reported to the IRB.

Serious Adverse Event Reporting

Serious adverse events (SAEs) are defined as:

- Life-threatening
- Fatal/Death
- Hospitalization/prolongation of hospitalization
- Congenital anomaly
- Persistent or significant disability/incapacity
- Required intervention to prevent permanent impairment/damage

SAEs must be tracked using the NIDA SAE form. The PI/Coordinator will report all SAEs in the annual report to NIDA, including any IRB recommendations on SAEs related to the study. All adverse events will be recorded and reported in aggregate on an annual basis to NIDA, as well as the IRB, and quarterly to the DSMB.

Any unexpected events will be reviewed by the Research Manager, in consultation with the PI, for determination as to whether it meets the definition of an Unanticipated Problem. If determined to be an Unanticipated Problem, or any of the following below, the issue must be reported to the IRB within 10 working days.

a. New Information that indicates a change to the risks or potential benefits of the research in terms of severity or frequency or impacts the subject's willingness to participate
b. Noncompliance: An action or activity in human subject research at variance with the approved IRB protocol, other requirements and determinations of the IRB, the HRPP Policy Manual and other applicable policies of Stanford University, SHC, LPCH, VAPAHCS

(e.g., VHA Handbook 1200.5), Palo Alto Veterans Institute for Research (PAVIR) or relevant state or federal laws. When the event is:

- Possibly serious: Noncompliance that affects the rights or welfare of human subject research participants.
- Possibly continuing: A pattern of noncompliance that continues to occur after a report of noncompliance and a corrective action plan has been reviewed and approved by the IRB, after an investigator has been warned to correct errors or noncompliance, or a circumstance in which an investigator fails to cooperate with investigating or correcting non-compliance.

c. Complaint unresolved by the research team
d. Incarceration when in the opinion of the PD it is in the best interest of the participant to remain on the study.
e. Other events or information: Examples include a deviation intended to eliminate an immediate hazard to a participant, suicide or suicide attempt of a participant, other Audit or Monitoring Visit reports and Corrective Action Preventative Action (CAPA) plans. Report only after consulting with the IRB Panel Manager.

Unexpected deaths or life-threatening experiences related to the research (at Stanford, or when STANFORD is the coordinating institution in a multi-site study) must be reported to the IRB within 5 working days from PD learning of event.

Unanticipated Problems Involving Risks to Participants or Others (UPs): Events (internal or external, deaths, life-threatening experiences, injuries, or other) occurring during the research study, which in the opinion of the Monitoring Entity or the PD meet all of the following criteria:

a) Unexpected

in terms of nature, severity, or frequency, given (a) the research procedures described in the protocol-related documents, and (b) the characteristics of the subject population being studied;

AND

b) Related to participation in the research or there is a reasonable possibility or likelihood that the incident, experience, or outcome may have been caused by the procedures involved in the research;

AND

c) Harmful: the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

All records of trial safety must be documented and stored in the “Trial Safety” folder of the STOP server.

Trial Monitoring

Adverse Events, Serious Adverse Events, Unanticipated Problems, and Protocol Deviations will be monitored on a continual basis and reported per information in the Study Events section.

Patient Adherence will be monitored as described in the relevant section, and in Compliance Monitoring section above.

The PI will hold regular staff meetings at least twice monthly to assess study team member understanding of responsibilities as per the Education section.

The first 10 participants will have case report forms and consent forms reviewed for accuracy and completion immediately after enrollment and entry into the follow-up period. After the first ten participants, case report forms and consent forms will be evaluated for completeness every 50 participants, or every 3 months. The results of these evaluations will be discussed at the quarterly DSMB meeting.

Participant Monitoring

The research team must check all active participants in REDCap at least once a week to identify any missing assessments, and to call participants with reminders to complete the assessments.

Data Safety and Monitoring Plan

Ultimately, the PI will be responsible for monitoring the safety and efficacy of this trial, executing the Data and Safety Monitoring (DSM) plan, and complying with the reporting requirements. In addition, Dr. Hah will conduct periodic internal reviews to monitor the trial with a rotating panel of 2 additional physicians, and 2 Stanford Systems Neuroscience and Pain Lab members. The Stanford Systems Neuroscience and Pain Lab members will have with no conflicts of interest with, or financial stakes in the research outcomes that would make them ineligible to participate in the internal review.

Frequency of DSM

The internal committee will analyze the DSM monitoring report every 3 months in the course of the trial. At minimum, Dr. Hah will meet with one member of the rotating internal panel every 3 months to evaluate the safety and efficacy of the trial, the execution of the DSM plan, and compliance with reporting.

Content of DSM Report:

A DSM report will be included in the annual progress report to NIDA and will include:

- Brief description of the trial
- Retention and disposition of study participants (including review of the study's progress toward recruitment goals, treatment adherence, participant attrition/retention rates)
- Q.A. Issues (including analysis of appropriate completion of forms)
- Regulatory Issues (including IRB regulatory actions and changes or amendments to the research protocol approved by the IRB)
- AEs
- SAEs

Case Report Form Completion

Missing data that is available through patient records such as EPIC will be recorded with a notation of such. Data discrepancies will be compared to any source data such as EPIC and corrections made by crossing out the original value, providing the correct value, dating, initialing, and providing a reason for the correction. If there is no hard copy, a comment should be made on REDCap. Missing data or data discrepancies that cannot be resolved by verifying source data will be left as missing.

Consent Form Completion

Consent forms will be evaluated for completeness of all signatures, required initials, and dates. Any missing signatures will be obtained by mailing the patient a copy of the consent form and requesting the signature with the current date. Any missing PI or staff signatures will be obtained and dated with the current date. Patients with missing signatures who are unable, or unwilling, to provide missing signature will be withdrawn from the study and data will not be used.

Electronic Data Verification

Electronic data is entered via the Stanford REDCap system or Perioperative CHOIR. Participants enter responses directly into the electronic system, unless they specifically request responding via phone calls. Hard-copy Case Report Forms are entered into REDCap manually by study staff, after they have completed instructional training and a mock-entry packet that is reviewed by the Research Manager, coordinator, or study monitor.

An additional 10% of data will be randomly verified by study staff prior to data analysis. Verification will occur via visual inspection. Discrepancies will be noted, original source data checked, and the correct value entered. All verified data will be noted with the reviewer's initials and date. Corrections will be noted with the date, initials, and reason for correction. Consistent errors will prompt a more comprehensive review of the data at the PI's discretion.

Primary Efficacy Outcome-Observation Arm

Time to opioid cessation, defined as the first of 2 consecutive reports of opioid cessation on the modified BPI.

Secondary Efficacy Outcomes-Observation Arm

1. Opioid misuse (This will be defined as a score of 9 or higher on the Current Opioid Misuse Measure).
2. Time to pain cessation (This will be defined as the first of five consecutive days of 0 average pain).
3. Time to recovery (First report of patient indicated "Yes" to having recovered from surgery).

Primary Efficacy Outcome-Intervention Arm

Time to opioid cessation, defined as 1st of 2 consecutive reports of return to baseline opioid dose or lower.

Secondary Efficacy Outcomes-Intervention Arm

1. Opioid misuse (This will be defined as a score of 9 or higher on the Current Opioid Misuse Measure).
2. Time to complete opioid cessation, defined as the first of 2 consecutive reports of opioid cessation on the modified BPI.
3. Time to pain cessation (This will be defined as the first of five consecutive days of 0 average pain).
4. Time to recovery (First report of patient indicated "Yes" to having recovered from surgery).
5. Treatment engagement is defined as participation in >50% of phone sessions.
6. Treatment initiation is defined as participation in at least 1 phone session.

Methods for handling missing data and non-adherence to protocol:

Subjects dropping out will be censored at the last known data point. Competing events such as a second surgery will be reasons for censoring at the time of the competing event. Missing data will not be imputed.

Modifications History

Last Updated 10/15/2020 by Luke Pirrotta, CRC.