# OPTIMIZING PAIN MANAGEMENT:

# A PILOT RANDOMIZED TRIAL IN PATIENTS UNDERGOING ARTHROSCOPIC SHOULDER SURGERY

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|---|---|
| Trial Code: | PMCB |
| Study Phase: | Clinical Phase IIA |
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**CONFIDENTIAL**

Nothing herein is to be disclosed without the prior approval of the sponsor.

**TABLE OF CONTENTS**

## LIST OF TABLES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| **ACE** | Angiotensin converting enzyme |
| **AE** | Adverse event |
| **ADL** | Activities of daily living |
| **ADR** | Adverse drug reaction |
| **ANOVA** | Analysis of variance |
| **APS** | American Pain Society |
| **ASA** | American Society of Anesthesiologists |
| **ASA** | Acetylsalicylic acid |
| **BID** | *Bis in die* (twice a day) |
| **Block** | Interscalene nerve block |
| **BPB** | Brachial plexus nerve block |
| **CI** | Confidence interval |
| **CIHR** | Canadian Institutes of Health Research |
| **COPD** | Chronic pulmonary lung disease |
| **COX-2** | Cyclooxygenase-2 |
| **CTCAE** | Common Terminology Criteria for Adverse Events |
| **DSQ** | Dossier Santé Québec |
| **eCRFs** | Electronic Case Report Forms |
| **EC** | Enteric-coated |
| **EDC** | Electronic data capture |
| **ER** | Emergency room |
| **eGFR** | Estimated glomerular filtration rate |
| **GA** | General anesthesia |
| **GCP** | Good Clinical Practice |
| **GI** | Gastrointestinal |
| **ICH** | International Conference on Harmonisation |
| **IMMPACT** | Initiative on Methods, Measurement and Pain Assessment in Clinical Trials |

| | |
|---|---|
| **IRB** | Institutional Review Board |
| **ITT** | Intention-to-treat |
| **IV** | Intravenous |
| **NIH** | National Institutes of Health |
| **mL** | Millilitres |
| **MA** | Meta-analysis |
| **MMA** | Multimodal analgesia |
| **NSAIDs** | Non-steroidal anti-inflammatory drugs |
| **OR** | Odds ratio |
| **PD** | Participant diary |
| **PHQ-4** | Patient Health Questionnaire-4 |
| **PM** | Product Monograph |
| **PMC** | Pre-emptive non-opioid multimodal pre-surgery medication cocktail |
| **PO** | Per os |
| **PONV** | Post-operative nausea and vomiting |
| **POP** | Postoperative pain |
| **POQ** | Patient Outcome Questionnaire |
| **PSEAT-CTA** | Protocol Safety and Efficacy Assessment Template – Clinical Trial Application |
| **QI / PI** | Qualified Investigator / Principal Investigator |
| **RCT** | Randomized controlled trial |
| **SAE** | Serious Adverse Event |
| **SC** | Study Coordinator |
| **SD** | Standard deviation |
| **SR** | Systematic review |
| **SSRIs** | Selective Serotonin Reuptake Inhibitors |
| **TPD** | Therapeutics Products Directorate |
| **UP** | Unanticipated problem |

## STATEMENT OF COMPLIANCE

This pilot randomized clinical trial will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), Institutional Review Boards (IRB) for St. Mary's Hospital (Montreal, Quebec), and other two enrolled sites (to be confirmed).

No deviation from, or changes to the protocol will take place without prior agreement from the sponsor, and documented approval from the IRBs, except where necessary to eliminate an immediate hazard to the trial participants.

I agree to ensure that all staff members involved in this study are informed about their obligations in meeting the above commitments.

Lead Investigators: Ana Miriam Velly, DDS, MSc, PhD and Moreno Morelli, MD, MSc. Orthopedic Surgeon

Signed: _____ Date: _____

Name: Ana Miriam Velly, DDS, MSc, PhD

Signed: _____ Date: _____

Moreno Morelli, MD, MSc. Orthopedic Surgeon

## PROTOCOL SUMMARY

**Title:** Optimizing pain management: A pilot randomized trial in patients undergoing arthroscopic shoulder surgery.

**Précis:** Postoperative pain (POP) affects quality of life, causes psychological distress, and increases the risk of persistent chronic pain. Poorly managed POP imposes a substantial economic burden on patients and Canada's health care system. A 2016 review concluded that more randomized controlled trials (RCT) are needed to evaluate multimodal analgesia (MMA) approaches to POP. Within an MMA regimen, opioids are common and have the highest profile for adverse effects. Opioid reduction strategies for POP management often include a brachial plexus nerve block (BPB), acetaminophen, and a non-steroidal anti-inflammatory drug.

In this multicentre pilot 2-arm parallel randomized controlled trial (RCT), 36 patients undergoing arthroscopic surgery for shoulder rotator cuff pathology or shoulder instability will be randomly assigned to a pre-surgery non-opioid multimodal medication cocktail including pregabalin and celecoxib and an interscalene nerve block (PMC+Block), or an interscalene nerve block (Block). The study control is the Block. Questionnaires will be completed before surgery, 6 hours, and at 1 day, 1 week, 2 and 6 months after surgery.

**Objectives:** The specific objectives of this pilot RCT are to:
1) Determine the feasibility of a large future definitive pragmatic RCT evaluating a non-opioid treatment regimen;
2) Identify solutions to methodological or practical challenges;
3) Determine the variance of outcome measures to assist with sample size calculation for the definitive RCT; and
4) Evaluate the tolerability of the study intervention.

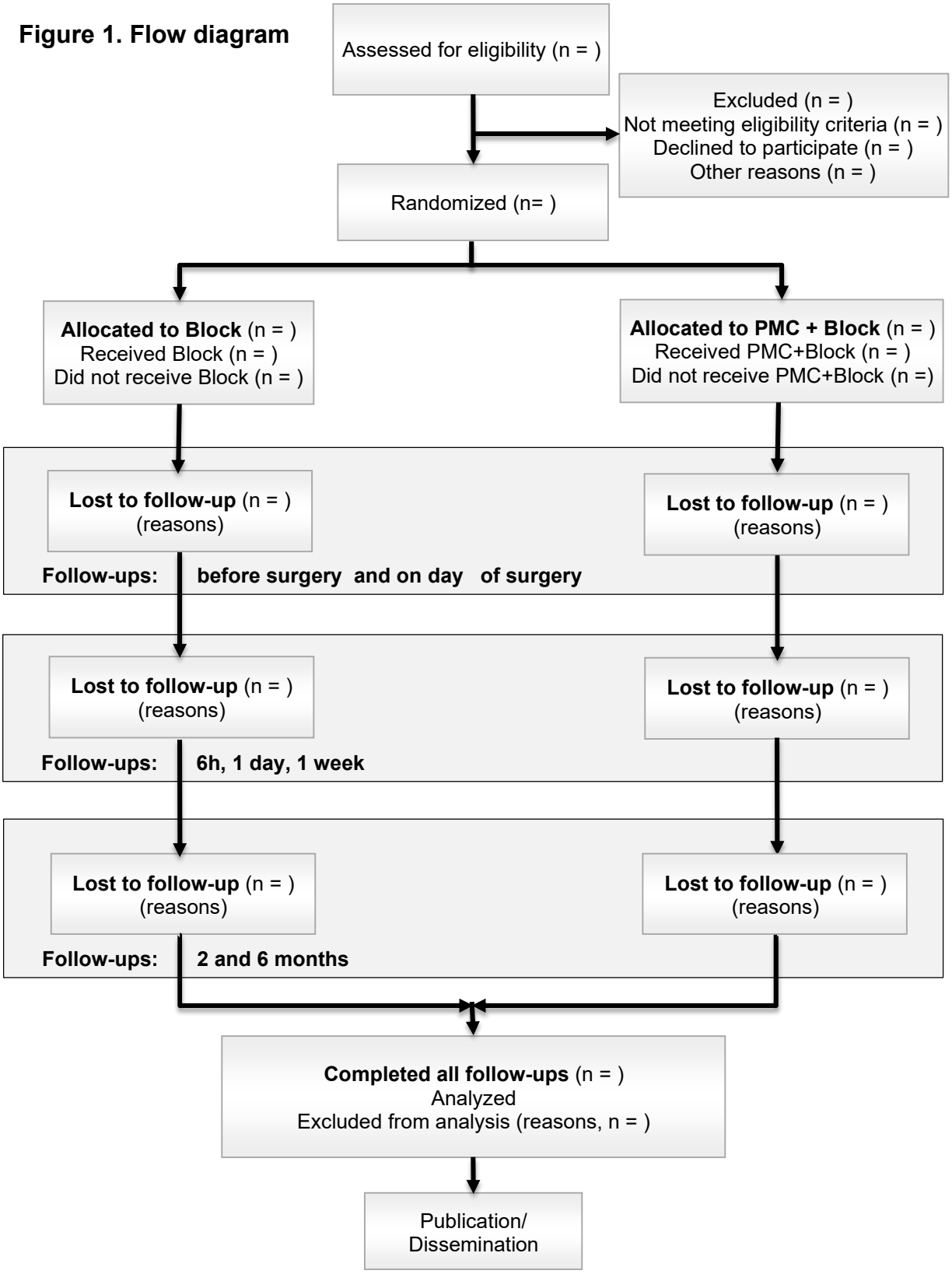
**Endpoints:** To assess feasibility and to identify solutions to challenges, we will elicit feedback from evaluators to record challenges. To estimate variance of outcome measures, pain management, pain intensity, physical activity, and disease-specific quality of life scores, will be evaluated. Safety assessments will include adverse event reporting.

**Population:** A total of 36 adult patients undergoing arthroscopic surgery for shoulder rotator cuff pathology or shoulder instability with at least 6 months of symptoms, will be recruited.

## PROTOCOL SUMMARY

| | |
|---|---|
| **Phase:** | Clinical Phase IIA.<br>This is a pilot RCT to assess the feasibility of a large RCT. |
| **Number of sites enrolling participants:** | Participants will be recruited from three participant hospitals:<br>St. Mary's Hospital, Montreal, Quebec<br>2) Other two participant hospitals (To be confirmed). |
| **Description of the study agent:** | The study agents are:<br>- Pregabalin (analgesic), oral: 25 mg.<br>- Celecoxib (analgesic), oral: 100 mg. In case of contra-indication or intolerance, Naproxen EC 500 mg will be used.<br>- Interscalene nerve block (Block; bupivacaine 0.5%, with epinephrine 5 µg/mL will be administered peri-neurally in a volume of 5 to 15 mL. |
| **Planned Study duration:** | Approximately 24 months (from start of screening to end of 6-month follow-up). |
| **Participant duration:** | Approximately 6 months after surgery. |
| **Statistical Analysis:** | Primary endpoints (feasibility criteria): Summary statistics and thresholds of acceptability for each criterion as follows: ≥ 30% for recruitment, % blinding (no threshold), adherence by ≥ 75% of participants, ≤20% for dropout, ≥80% for response rates, and ≤ 25% time needed to collect data will be estimated.<br><br>Safety: Descriptive statistics: absolute frequency and percentage of the adverse events will be calculated. |
| **Hypothesis:** | This pilot RCT does not test a hypothesis. |

**Figure 1. Flow diagram**



## 1. KEY ROLES AND CONTACT INFORMATION

**The role of each principal applicant and co-applicant proposed.**

Table 1 lists the members of this study, as well as their roles and affiliations.

**Table 1. Members of the Research Team, Role and Location**

| Team member | Title | Institution, address & phone number |
|---|---|---|
| Dr. Ana Miriam Velly, MSc, PhD<br>ana.velly@mcgill.ca | Lead Investigator<br>(Co-PI)<br>Epidemiologist | Jewish General Hospital<br>3755 Cote Ste Catherine, Suite A.017<br>514-340-8222 ext. 22932 |
| Dr. Moreno Morelli, MD, MSc<br>moreno.morelli@mcgill.ca | Lead Investigator<br>(PI)<br><br>Orthopedic Surgeon<br>Site Investigator | St. Mary's Hospital<br>3830 Av. Lacombe, Room 2304<br>514-848-3317 |
| Dr. Ian Shrier, MD, PhD<br>ian.shrier@mcgill.ca | Epidemiologist<br>Co-investigator | Jewish General Hospital<br>3755 Côte Ste-Catherine<br>514-340-8222 ext. 7563 |
| Dr. Robert Platt, PhD<br>robert.platt@mcgill.ca | Statistician<br>Co-investigator | Jewish General Hospital<br>3755 Côte Ste-Catherine, Suite H485<br>514-340-8222 ext. 28683 |
| Dr. Joel Katz, PhD<br>jkatz@yorku.ca | Psychologist, Pain specialist<br>Co-investigator | York University<br>200 Elizabeth Street, 3EN-464<br>416-736-2100 ext.40557 |
| Dr. Greenberg | Anesthesiologist | St. Mary's Hospital<br>3830 Av. Lacombe, Room 2304<br>514 345 3511 Ext: 3282 |
| Dr. Gina Wu | Anesthesiologist | St. Mary's Hospital<br>3830 Av. Lacombe, Room 2304<br>514 345 3511 Ext: 3282 |

Drs. Velly and Morelli (nominated Lead PI and Co-PI), respectively affiliated to the Jewish General Hospital Lady Davis Research Institute, and St. Mary's Hospital are responsible for overseeing the study. Dr. Velly is an epidemiologist with experience and expertise in pain-related clinical trials and cohort studies. Dr. Morelli is a renowned surgeon with extensive experience in arthroscopy shoulder surgery and pain management.

Dr. Morelli is also the site Qualified investigators (QI/PI) from St. Mary's Hospital.

Dr. Morelli will be engaged in performing the surgery on patients. The anesthesiologists Dr. Greenberg and Dr. Wu will be involved in performing anesthesia. Dr. Shrier is an epidemiologist and methodologist. He participated in designing the study and will be involved in

the day-to-day management of the study with Dr. Velly, identifying challenges that arise and developing appropriate solutions. Dr. Platt is a professor of biostatistics with special expertise in clinical trials. He was the Scientific Officer for one of the CIHR RCT committees for three years and will oversee trial methodology. Dr. Platt has guided the statistical analysis plan. He will supervise all analyses once the data have been collected and will provide additional methodological support and ideas for solutions when challenges arise. Dr Katz has been conducting RCTs in pre-emptive and preventive analgesia for the past 30 years, including studies assessing pregabalin and celecoxib. He provided input on the study methodology and will provide additional methodological support.

# 2. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 2.1. Background Information

Almost four in five surgical patients experience moderate to severe acute postoperative pain (**POP**) (1,2). Severe chronic POP affects 2 to 10% of patients (3,4). POP is often poorly managed, compromising healing and increasing morbidity (5), in spite of new standards, guidelines, and education efforts (6-9). Inadequate POP management disturbs quality of life, raises psychological distress (10), and increases the risk of persistent POP (11,12). Poorly managed POP imposes a substantial economic burden, not only for the patient, but also for Canada's health care system (13). In a 2011 Lancet article, Wu and Raja emphasized that "undertreatment of acute POP has been widely recognized as an important issue", with no consensus on how best to manage POP (6); **this remains true today** (7).

In 2017, Rai *et al.* described that the standard perioperative analgesics comprise acetaminophen/paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids (12). Currently, excessive opioid use is topical in the public press and academic literature. The opioid "epidemic" results in potential for abuse, addiction/dependence and adverse events (AE) including death (14-19). According to a 2017 Health Quality Ontario report (20), 2 million people (14% of the population), filled 9 million opioid prescriptions in 2016, many of which were for POP management. In Canada and elsewhere, opioid use for POP management is extensive (17,19,21,22). Orthopedic surgeons account for 51.4% of all opioid prescriptions dispensed in Canada (22). Opioids such as oxycodone and hydromorphone are standard perioperative analgesics used in Canada. It is estimated that approximately 3% of elderly opioid-naïve patients will be on opioids for longer than 3 months after major surgery (23,24). Due to the actual number of surgeries performed, this seemingly small percentage represents a large number of individuals (25). Escalating reports of opioid overdose deaths are often related to medications not routinely prescribed for POP (e.g., fentanyl) (25). The extent of opioid misuse secondary to POP prescriptions is difficult to quantify.

Regional anesthesia (nerve blocks) may reduce opioid use and is gaining popularity in Canadian institutions (6,7). This approach is encouraged by the American Pain Society **(APS)**, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee **(ASA)** on Regional Anesthesia, Executive Committee, and Administrative Council panel (7), but there are limitations to this modality. The benefit is greatest in the first 12-16 postoperative hours, when pain scores are reduced as is opioid consumption. However, as the block wears off, pain increases, and opioids are required (26). Nerve blocks have an associated cost, and expose patients to the risk of neurological injury, respiratory compromise for some, and rebound pain with block resolution (26).

Multimodal analgesia (**MMA**), which may include regional anesthesia and pharmacologic therapy, has been suggested to be an effective treatment for POP (6,7,16,27)]. MMA is defined as the use of different analgesic drugs (e.g., gabapentin or pregabalin, NSAID and/or acetaminophen) and techniques (e.g., regional anesthesia), targeting different mechanisms of action in the peripheral and/or central nervous system. Within an MMA regimen, however, opioids are still

common prescribed despite being associated with the highest risk of AE (e.g., nausea, constipation, respiratory depression, potential for addiction).

The APS-ASA panel (7), RCTs (28,29), systematic reviews (**SR**), and/or meta-analysis (**MA**) (30-32) concluded that more RCTs should be conducted to evaluate approaches to POP management. Also, the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (**IMMPACT**) stated "Although prevention of chronic pain would have substantial public health benefits, few preventive interventions have been developed" (33).

Thus, there is an urgent need to find an effective non-opioid medication regimen as an alternative strategy to reduce opioid use and provide effective POP management. In this pilot RCT the name and description of the study agents are described below.

## 2.2. Overall Objective and Rationale

In view of the urgent need to find an effective non-opioid medication regimen as an alternative strategy to decrease opioid use and provide effective POP management, the overall objective of this pilot RCT is to test the feasibility and methods to help plan a future definitive pragmatic 2-arm RCT (specific objectives of this pilot RCT are described in more detail in Section 3). In this pilot RCT, participants will be randomized to the following **trial intervention groups**:

-
- **PMC + Block** (Pre-surgery medication cocktail plus interscalene nerve block), or
- **Block** (Interscalene nerve block).

The rationale for the selection of these interventions is described below.

### 2.2.1. Pre-surgery medication cocktail pregabalin and celecoxib

- **Pregabalin**

We decided to include **pregabalin** since there is moderate-quality data supporting its use in the **MMA** approaches to POP (7). SRs and/or MAs also provide evidence for the benefits of pregabalin including: (i) *greater promise in preventing the conversion from acute pain to chronic* (30); (ii) *fewer AE* (31); and (iii) *preoperative use of pregabalin was efficacious in reduction of postoperative pain, total morphine consumption, and the occurrence of nausea following spine surgery* (32). RCTs conducted by members of the present team (Dr. Joel Katz) as well as others demonstrated that **compared with placebo** perioperative pregabalin reduces **opioid consumption** (34-39) and **POP intensity** (34,37-41). SRs and/or MAs found that pregabalin significantly decreases **opioid consumption** (31,32,42-45), **POP intensity** (28,31,32,42), and **AE** (e.g., nausea, vomiting, opioid AE) (32,43,44,46). Studies also suggested that perioperative pregabalin diminishes chronic **POP** (28,30,45,47). The Clarke *et al.* MA (30) that included 3 pregabalin and 8 gabapentin RCTs, revealed a greater pregabalin effect decreasing the likelihood of chronic POP development (Odds Ratio [**OR**] = 0.09; 95%CI: 0.02-0.79, P = 0.007) than gabapentin trials (OR = 0.52, 95%CI: 0.27-0.98, P = 0.04). An RCT in Canada, however, did not find a statistically significant difference between perioperative administration of pregabalin and celecoxib versus placebo and celecoxib at 2 hours before total hip arthroplasty on the incidence of chronic POP (34).

- **Celecoxib**

A Cochrane review that included dental surgery studies and one orthopedic study (48) found that 35% of patients receiving celecoxib (COX-2 selective nonsteroidal anti-inflammatory drug [**NSAID**]) reported at least 50% POP relief over a period of 4 to 6 hours after surgery. In total knee replacement, perioperative celecoxib reduced POP and the need for opioids (49). In patients having total knee replacement, spinal surgery, and some non-orthopedic surgeries, preoperative celecoxib reduced POP, analgesic consumption and increased patient satisfaction. However, there was no decrease in nausea, vomiting or recovery from surgery (50). A RCT of total knee arthroplasty patients found that celecoxib led to less POP on days 2 and 3, improved early range-of-motion and required significantly less opioids than the patient controlled analgesia with morphine group (51).

#### 2.2.2. Interscalene nerve block with bupivacaine

**Bupivacaine** is indicated for the production of local or regional anesthesia and analgesia with the following procedures: local infiltration procedures, **peripheral nerve blocks (**also referred to as a brachial plexus block), retrobulbar blocks, caudal, epidural, and subarachnoid (spinal) blocks (see Bupivacaine Product Monographs).

The American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council panel, encourage the use of regional anesthesia (nerve blocks) since it may reduce opioid use and POP (7).

### 2.3. Potential Risks and Benefits

#### 2.3.1. Known potential risks of the trial interventions

*Note that Appendices I-II and IV-V are referenced from the corresponding Product Monographs (PM).*

##### *2.3.1.1. Pre-surgery medication cocktail pregabalin/celecoxib trial intervention*

- **Pregabalin**

The most common AEs of pregabalin are somnolence, dizziness, peripheral edema, dry mouth, blurred vision, constipation, disturbance in attention, forgetfulness, weight gain, muscle weakness, nausea. They are usually mild to moderate in intensity.

In this current pilot RCT:

- The maximum daily dose of pregabalin (75 mg BID, 150 mg/daily) will only be prescribed for a short period (Section 6.1.5). The AE are more common among patients receiving doses of 300 mg/daily or higher (Appendix I).
- At preoperative phase, pregabalin dose will be escalated. After surgery, pregabalin will be tapered as of the 6th post-operative day to prevent AE associated with abrupt or rapid discontinuation (e.g. insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea).

- In case of any AE, the dose for pregabalin will be tapered to the highest tolerable dose.

Participants suffering from serious adverse events (**SAE**) will be directed to the emergency room (**ER**) for appropriate supportive measures. Appendix I- Table 6 lists the recommended actions for pregabalin discontinuation and supportive measures as described by Pregabalin PM.

- **Celecoxib and Naproxen**

Gastrointestinal, cardiovascular and other AE are listed in Appendix II. SAE such as myocardial infarction, stroke, thrombotic events and renal failure are more frequently associated with doses higher (>200mg) than what is used in this study (200 mg/daily – see Section 6.1.5).

#### *2.3.1.2. Interscalene nerve block with Bupivacaine*

Nerve blocks expose participants to the risk of neurological injury, respiratory compromise for some, and rebound pain with block resolution (see Appendix III and Appendix IV, and Section 6.1.5).

#### *2.3.1.3. Drug specified by Health Canada but is not a trial intervention drug*

- **Dexamethasone**

In this pilot RCT, a **single dose** of dexamethasone will be provided through the interscalene nerve block, except for short-term elevation in blood glucose and euphoria. Note that administration of dexamethasone is part of standard procedure (see Section 7.1.2).

Patients with diabetes will have their blood glucose tested and appropriately managed pre and post-operatively since they are more likely to have elevated blood glucose. Additionally, the dose used in this study (dose 2 mg) is very unlikely to result in euphoria. Patients will be placed and observed in the post-anesthetic unit for a duration of 60 to 90 minutes. Please refer to the corresponding Product Monograph for an extensive list of potential AEs (Appendix V).

## 2.4. Rationale for the Necessity of Exposing Human Participants to Such Risks

Suboptimal management of POP has been widely recognized as an important issue", with no consensus on how to best manage it (5-9). Moderate to severe acute POP is common (1,2) and if not well treated, increases the risk of chronic POP (11,12). POP disturbs quality of life and raises psychological distress (10). The American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council panel (7), RCT's findings (28,29), SR, and/or MA (30-32) recommended that more RCTs should be conducted to improve POP management and prevent chronic POP (33).

This pilot RCT will provide important knowledge to contribute to the advancement of pain management after arthroscopic shoulder surgery. For extensive details on the rationale of the study, please refer to Sections 2.1 and 2.2.

## 2.5. Why the Value of the Information to Be Gained Outweighs the Risks Involved

Although we cannot guarantee that patients' recovery from surgery will be better with one treatment as compared to another, their participation in this pilot study will enable us to evaluate the feasibility for a larger RCT which aims to address the best methods for POP management.

## 2.6. If Risk Is Related to Proposed Procedures Included in Protocol, Any Alternative Procedures that Have Been Considered and Explanation on Why Alternative Procedures Not Included

### 2.6.1. Pre-surgery medication cocktail pregabalin/celecoxib trial intervention

- **Pregabalin**

Our decision to select pregabalin instead of gabapentin is supported by the greater effectiveness obtained following orthopedic surgery (29), and greater absorption profile and bioavailability with pregabalin when compared to gabapentin (52).

- **Celecoxib**

We decided to use celecoxib instead of nonselective NSAIDs because it is associated with fewer AE (53-55), including gastrointestinal complications (56). This is very important in this study, since patients need to be fasting for surgery and their appetite does not typically return immediately after surgery.

Potential participants will be excluded if they cannot receive either pregabalin, or both Celecoxib and naproxen EC (see Section 5.2).

### 2.6.2. Interscalene nerve block with Bupivacaine trial intervention

Bupivacaine will be primarily used for the peripheral anesthesia (Block). (see Section 6.1.5). Participants will be excluded if they cannot receive bupivacaine (see Section 5.2). They are not off label since **bupivacaine** is indicated for **peripheral nerve blocks, also referred to as a brachial plexus block** (see Bupivacaine Product Monographs). During the pilot study, participants will receive an interscalene peripheral nerve block, with doses that are within the recommended doses.

The American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council panel, encourage the use of regional anesthesia (nerve blocks) since it may reduce opioid use and POP (7).

### 2.6.3. Drug specified by Health Canada that is not trial intervention

All patients will receive dexamethasone to control nausea and vomiting. No alternative drug will be used (see Section 7.1.2).

## 2.7. Known Potential Benefits

### 2.7.1. Pre-surgery medication cocktail pregabalin/celecoxib trial intervention

- **Pregabalin**

Studies provide evidence for the benefits of pregabalin that include reducing POP (28,31,32,34,37-42); reducing opioid consumption (31,32,34-39,42-45) and diminishing chronic POP (28,30,45,47).

- **Celecoxib or naproxen**

The benefits of celecoxib include reduction of POP (48,49,51) and reduction of analgesic consumption (49-51). Naproxen is commonly used for the relief of minor aches and pains in muscles, bones and joints, mild to moderate pain accompanied by inflammation in musculoskeletal injuries (sprains and strains), and primary dysmenorrhea (Naproxen PM).

### 2.7.2. Interscalene nerve block with Bupivacaine trial intervention

The American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council panel (7) encourage the use of regional anesthesia (nerve blocks) since it may reduce opioid use and POP (6,7). This approach is gaining popularity in Canadian institutions.

### 2.7.3. Drugs specified by Health Canada that it is not a trial intervention

- ***Dexamethasone***

Dexamethasone is used in ambulatory patients to decrease the incidence of post-operative nausea and vomiting **(PONV)** (57), as well as to improve pain management, and prolong the duration of the peripheral nerve block (58,59).

## 3. OBJECTIVES

The **primary objective of this pilot RCT** is to **test the feasibility and methods** to help plan a future definitive pragmatic 2-arm RCT (Block, PMC+Block).

The **specific objectives** of the proposed **pilot study** are to:

- Determine the feasibility of a future definitive pragmatic multi-centre RCT;
- Identify challenges within the proposed RCT and develop solutions;
- Determine the variance of outcome measures for future sample size calculation for the definitive future pragmatic RCT; and
- Evaluate the tolerability of the study intervention.

The secondary objective is to estimate secondary outcomes (e.g. pain intensity and opioid consumption) between two treatment groups.

For details of the study outcomes, please refer to Section 4.2.1 and Tables 2-3.

# 4. STUDY DESIGN AND ENDPOINTS

## 4.1. Description of Study Design and Study Population

### 4.1.1. Study design

This is a **2-arm pilot RCT** (Figure **1**) in which participants undergoing arthroscopic surgery for shoulder rotator cuff pathology or shoulder instability, with at least 6 months of symptoms will be randomized to either of the following 2 groups:

- **PMC+Block** (Pre-surgery medication cocktail plus interscalene nerve block), or
- **Block** (Interscalene nerve block).

Section 6.1.5 describes the **scheduled dosage** for each planned trial intervention drug used.

### 4.1.2. Study population

We will recruit 36 participants undergoing arthroscopic surgery for shoulder rotator cuff pathology or shoulder instability, with at least 6 months of symptoms. Eligibility criteria are described in Sections 5.1 and 5.2. We intend to recruit patients of six participating orthopedic surgeons at three orthopedic clinics from 3 from the following participating hospitals:

- **St. Mary's Hospital: 3830 Av. Lacombe, Montreal, Quebec**;
- **Two participant hospitals (To be confirmed)**

Six patients will be recruited per surgeon (12 per institution). In general, each surgeon approximately 12-16 eligible patients per month. Our 25% recruitment rate (3-4 patients/month) is conservative when compared to other Canadian RCTs from 2010 to 2016 that also assessed the effect of pregabalin in: laparoscopic cholecystectomy (60); total hip arthroplasty (34,61); thoracotomy (62); as well as other treatments for POP management (63), where the recruitment proportion ranged from 59% to 88%. We believe 25% is reasonable since: (i) there is minimal extra time commitment; and (ii) long-term follow-up data will be coordinated with standard post-surgical care visits.

We decided to include three centres to identify challenges with conducting a multi-centre trial as recommended by CIHR reviews, since the eventual definitive trial will include more centres. We considered using only two institutions but felt there was a risk of missing important challenges due to inter-hospital variation. We also considered using four institutions. However, that would mean recruiting only 9 patients per institution (36 total number of patients/4 institutions), and either: 1) our estimates for each cluster (institution) would be less reliable; or 2) we would have to recruit additional patients at additional cost. We therefore chose three institutions as an appropriate compromise.

For details on the study enrolment and follow-up, please refer to Section 5 and Section 7.

#### 4.1.3. Data collection

After recruitment, evaluators (research nurse or assistant) will collect the baseline data (Section 7.3.1).

During follow-up, an evaluator blinded to group assignment will call participants 6 hrs,1 day, 1 week, and 2 and 6 months after surgery to assess pain intensity with the POQ (67,68). At 2 and 6 months after surgery, evaluators will also assess physical activity with the POQ. A different evaluator (not involved in pain assessment), will call participants to assess AE and if they received **opioid and non-opioid supplemental pain management** (rescue medication, other treatments).

In addition, during in-office visit(s), evaluators will assess pain intensity and physical activity at the 2 and 6-month follow-ups data (see Section 4.2, Tables 2-3), if they had not yet been completed.

Data will be collected with tablets through an electronic data capture (EDC) system. All participant data collected will be stored in the EDC repository, where it will be reviewed and cleaned up, if necessary, by evaluators and study coordinator. This data will then be organized and exported into the study databases for analysis and reporting.

#### 4.1.4. Overview of study schedule

- **Training**. Evaluators, Study Coordinator (SC), site PI/QI, and PI will receive training on the operation of the EDC before they are authorized to begin enrolling study patients.
- **Data acceptability and compatibility**. The EDC system used to collect participant and evaluators data will be assessed for acceptability and compatibility prior to administration of any questionnaires.
- **Recruitment**. Potential participants who are interested in participating in the study will undergo consent procedures. Once they sign the consent form, they will be screened using the *Screening form* that comprises the inclusion and exclusion criteria (see Sections 5.1 and 5.2). If eligible they will be recruited to the study. An in-office potential participant log (Screening/enrolment log) will be kept recording the reason patients are excluded or declined to participate.
- **Randomization**. Participants will receive their randomized assignment after being eligible for participation into the study (Section 7.3.1).
- **Data collection**. Participants will complete the Participant diary (PD) before and after surgery (Sections 7.3.1 and 7.3.2). In addition, the evaluators will record details on the recruitment log and follow-up daily.

The Lead PI, the three site PI/QIs, the evaluators and the epidemiologist (Dr. Shrier) will meet the study team on a weekly basis throughout the recruitment and follow-ups to review the study outcomes Tables 2 and 3.

Study will be closed when all data including queries are cleaned, and analyzed. This may take 6 months after the last follow-up.

## 4.2. Study Outcomes

### 4.2.1. Primary outcomes

To assess the study feasibility and to identify solutions to challenges, we will elicit feedback from evaluators on feasibility indicators (Table 2) and we will record challenges of the study. To estimate variance of outcome measures, pain management, pain intensity, physical activity, and disease-specific quality of life scores, will be evaluated. Safety assessments will include AE reporting.

Tables 2 and 3 describe the feasibility indicators (primary outcome) and secondary outcomes of this pilot RCT.

**Table 2. Feasibility indicators**

- **Recruitment and consent**: If patient recruitment is below 25% early in the process, we will develop methods to improve recruitment (e.g., advertising, training, decreasing the barriers to recruitment). If at least 25% of eligible patients are recruited after implementing solutions, we will consider the study feasible because it would allow for ~4 patients per month per surgeon.
- **Treatment allocation randomization, blinding**: Problems will be summarized through internal communications. We will assess evaluator unblinding after the trial, and whether it was caused by study processes (solutions would be implemented during the pilot trial), active treatment efficacy or AE (64).

**Adherence**: We will document challenges and the proposed solutions with all participating surgeons through internal communications. If we cannot increase adherence (defined as taking at least 50% of the medication as prescribed 5 days before surgery) to occur in at least 75% of participants, we will consider the definitive trial to be non-feasible. POP medication is not part of intervention and is unrelated to "adherence". According to the clinical experience of St. Mary's PI site investigator (Dr. Morelli), there are exceptional instances where patients do not take the medication as prescribed. This usually happens when a patient is scheduled at the last minute and doesn't have enough time to start the medication regimen 5 days prior to surgery. Other than the aforementioned, there might be 1 patient per year who forgets to take the medication or never received their prescription on time. The estimate would be that over 90% of patients will take their medication as prescribed.

- **Dropouts**: We will assess the dropout rate during the study. We will document challenges and the proposed solutions with all dropouts through internal communications. We consider a dropout rate of ≤ 20% to be the threshold for a feasible future definitive RCT. This dropout is close to that of another pregabalin Canadian RCT (34,61). We expect minimal loss on follow-up for our planned primary outcomes in the future definitive RCT, since they will be assessed within 1 week after surgery, and require only 5 minutes of patient time during a phone call. We only expect a maximum of 20% loss to follow-up for

**Table 2. Feasibility indicators**

the 2- and 6-month evaluations because they are coordinated with the standard clinical follow-up visit that almost all patients attend.

- **Response rates to questionnaires and incomplete questionnaires**: We will consider 80% as an acceptable threshold. We will ask non-responders why they did not complete the questionnaires or the question and use this information to decide how to improve response rates. Questionnaires are listed in Table 3.
- **Time needed to collect data**: We will record how long each set of questionnaires requires and elicit feedback as to its acceptability. If more than 25% of patients consider the time unacceptable, the definitive RCT will focus on the most important data.
- **Frequency of AE and serious AE**: It will be recorded during study follow-up.

All these thresholds were based on discussions by team experts, since we did not find published consensus specifications for these values to assess study feasibility**.** Further, all these indicators will be discussed weekly between Lead PIs (Drs. Velly and Morelli), epidemiologist (Dr. Shrier), research coordinator, and evaluators (research assistants and research nurses).

Further, we will collect preliminary data as per Table 3 to assess the feasibility of recording the primary and secondary outcomes for the future definitive RCT, as recommended by the APS Committee on Quality Assurance Standards (65) and the IMMPACT (64,66). This data will also be used in sample size calculations for the definitive RCT.

**Table 3. Secondary outcomes**

- **Cumulative consumption of opioids for pain management**: We will assess if patients use opioids before surgery, and at 6 hours, 1 day, 1 week and 2 and 6 months after surgery.
- **Pain intensity post-surgery**: We will measure POP intensity before surgery, and at 6 hours, 1 day, 1 week and 2 and 6 months after surgery using the standardized, validated APS Patient Outcome Questionnaire"(POQ) (67,68). The pain intensity will be measured by the average of four values: the current pain after surgery, and the worst, least and average pain after surgery. The pain scale is presented as a row of equidistant numbers where 0 = "no pain" and 10 = "worst pain possible".
- **Supplemental pain management**: We will assess if patients received non-opioid supplemental pain management (rescue medication, other treatments) before surgery, and at 6 hours, 1 day, 1 week and 2 and 6 months after surgery.
- **Physical Activity**: We will use the validated self-assessment portion of the POQ (67,68). This questionnaire will be used at before surgery, and at 2-and 6-months post-surgery.

# 5. STUDY ENROLLMENT AND WITHDRAWAL

## 5.1. Inclusion Criteria

Eligible participants must meet all the following criteria:

- Require arthroscopic surgery for shoulder rotator cuff pathology or shoulder instability with at least 6 months of symptoms
- Male or female of 18 to 64 years of age
- Be willing to comply with all study procedures and be available for the duration of the study
- Provide dated and signed informed consent

## 5.2. Exclusion Criteria

A potential participant who meets any of the following criteria will be excluded from participation in this study:

- Allergies to any of the following drug combinations:
    - pregabalin, or
    - both celecoxib and naproxen EC; or
    - bupivacaine
- Allergic-type to reactions to sulfonamides
- History of asthma, urticaria, or allergic-type reactions after taking Acetylsalicylic Acid (ASA) or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance-rhinosinusitis, urticaria/angioedema, nasal polyps, asthma);
- Angioedema
- Bleeding disorders
- History of ulcers
- Inflammatory bowel disease
- Cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax)
- Ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction and/or angina)
- Congestive heart failure (NYHA II-IV)
- If liver impairment requires an adjustment of the dose of the study medication, then the patient will be excluded from the study
- Renal impairment (Renal impairment is identified by an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 $m^2$. This valued is estimated from a

calculator found at https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation)

- Known hyperkalemia
- Chronic pulmonary lung disease (COPD)
- Contraindications to pregabalin, or both celecoxib and naproxen EC; or bupivacaine
- Current use of high-dose opioids (>60 mg equivalents of morphine), gabapentinoids, antidepressants, antipsychotics, or cannabinoids
- Cancer
- Pregnancy or lactation. All females under age 55 get pregnancy tests prior to surgery. If they are pregnant, the surgery is cancelled. This procedure is not specific to this study, but a standard practice for all hospitals before surgery.
- Frail or debilitated patients
- Life expectancy of less than one year
- Those without DSQ (Dossier Santé Québec) or ClinicalConnect (Ontario) access
- Cannot be randomized to receive an interscalene block
- Patients who refused to do a blood test.
- Patients with BMI < 19 will be excluded
- Unable to communicate in English or French

## 5.3. Strategies for Recruitment and Retention

### 5.3.1. Screening and recruitment

All patients presenting to for their clinic appointment for shoulder surgery will be considered for enrollment.

Patients who come in for their appointment to the Orthopaedic Clinics (Initial evaluation by the surgeon before booking for surgery) will receive a study information sheet from the clinic staff. These details will also be posted publicly for patients to read as well as on the Ortho website. If patients are interested in participating, they can call the number on the sheet to reach a member of the Ortho Research Team or email the research program co-ordinator for more details. The research program co-ordinator and surgeon will not be interacting with patients directly, only the evaluator responsible for recruitment and data collection will be introducing the study to interested patients. Patients who agree will be scheduled an appointment with the evaluator. Patients will not be directly contacted for recruitment through the hospital surgery lists. After an initial period (1 month – 6 weeks), if no patients have contacted the research team, an application will be made to receive pre-operative patient lists from the hospital to facilitate direct recruitment.

During the appointment, the evaluator will explain the research study to the potential participant and ask if she/he would be interested in participating. If so, the evaluator will ask them to read the consent form, answering any questions she/he may have before signing the form. Once

potential participants sign the consent form, the evaluator will ask a few questions to ascertain their eligibility to participate in this study (Sections 5.1 and 5.2). If the patient is found eligible, the evaluator will provide a study summary sheet outlining the goals and objectives and the detailed consent form for review. After eligibility is confirmed, the potential participant is then enrolled. The target sample size is **36 participants** undergoing arthroscopic surgery for shoulder rotator cuff pathology or shoulder instability, with at least 6 months of symptoms; **12 participants will be recruited from each clinic**:**St. Mary's Hospital:** 3830 Av. Lacombe, Montreal, Quebec**; Two other participant hospitals (To be determined).**

In this pilot RCT, the sample size will not be adjusted for participation and dropout rates. We will measure the participation and dropout rates during the study to assess the feasibility of the large RCT. We will evaluate strategies to improve the participation rate.

#### 5.3.2. Retention

Participant's retention is important to this RCT. A combination of strategies will be utilized to maximize retention.

- After recruitment, the evaluator will ask eligible participants to complete questionnaires for the baseline assessment (Section 7.3.1) and what will be the best time to make the follow-up calls. Participants will be called at their specified best time before surgery if they do not respond to baseline questionnaires. Additional phone calls will be made if the first one is not answered.
- The evaluator will call participants to remind them to take the required medication before surgery (seven days before PMC onset).
- The evaluator will call participants before (Days 3 and 5) and after surgery (Days 6, 7, 13, 66 and 186) to evaluate how they are doing. They will be called again at other days if they do not respond to scheduled calls. Reporting to the follow-ups by phone may help decrease the dropout rate as compared to requesting patients to come to the hospital to complete the questionnaires or to ask them to complete paper questionnaires and send them by mail (Section 7.3.2).
- On the day of the surgery (Day 6), evaluators will ask participants to monitor the planned trial interventions as well as AE.
- To decrease the chance of missing the follow-up data assessment, participants will be contacted by phone prior to the 1-week (Day 13), 2- and 6-month (Days 66 and 186) follow-ups, to remind them about the scheduled time and to find an alternative time for follow-up/phone calls, if necessary. Additional phone calls will be made if the first one is not answered. Scheduling margins of 3 days before or after the 1-week, 2- and 6-month follow-ups will be offered to accommodate the patient's availability.
- At the 2- and 6-month post-surgery follow-ups at the orthopedic outpatient clinic, the evaluator will also ask participants to complete the questionnaires if they had not yet been completed.

## 5.4. Participation Withdrawal or Termination

### 5.4.1. Reasons for withdrawal or termination

Participants may withdraw voluntarily from participation in the study at any time upon request, including at baseline and at any follow-up time points.

An investigator may end an individual participation in the study if:

- Participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation. All participants who provide consent and are randomized to one of the treatment arms will remain in the study even if they are not able to follow through with their group assignment.
- If an enrolled participant declines to provide any of the essential baseline data (Section 7.3.1). This decision will be considered a voluntary withdrawal from the study by the participant and the PI will withdraw the participant from the study.

### 5.4.2. Handling of participant withdrawal or termination

All participants randomized to one of the treatment arms will continue to provide data unless and until they explicitly withdraw their consent for further data collection. Therefore, only participants who no longer consent to provide data will be excluded from further data collection.

Evaluators will only attempt to continue collecting follow-up data for participants who have withdrawn due to an unanticipated problem (**UP**) or other safety concerns. In such cases, only data related to the completion of reporting requirements for the UP will be recorded.

Participants withdrawn from the study for any other reason will not have any further data collected except for the date and reason for withdrawal.

All participants who withdraw from the study may continue to receive usual care as patients of the participating surgeons. Replacing participants who withdraw or whose participation is terminated from the study will not be allowed in this pilot RCT.

## 5.5. Premature Termination or Suspension of Study

### 5.5.1. Reasons for withdrawal or termination

This study may be prematurely suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the lead investigator (Drs. Velly and Morelli) and site PI/QI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.

# 6. STUDY AGENT

## 6.1. Study Agent(s) and Control Description

### 6.1.1. Acquisition

#### *6.1.1.1. Pre-surgery medication cocktail pregabalin/celecoxib trial intervention*

Participants will obtain pregabalin, celecoxib or naproxen EC from their hospital site pharmacy. Surgeons will include in the prescriptions a request that the pharmacist consult the Dossier Santé Québec (DSQ) in Quebec or the Health Network System in Ontario (to be confirmed). The pharmacist will consult the DSQ to verify that the patient is not on any other medication that would be a contra-indication to the study medication.

All patients are required to complete a health questionnaire when they consent for surgery. At that time, the surgeons will be able to determine co-morbidities that exist. However, the physicians do not necessarily know what potential interactions might exist between the study medications and those that the patient is already taking.

The hospital pharmacist will double check concomitant medications and evaluate interactions and contraindications.

#### *6.1.1.2. Interscalene nerve block with bupivacaine trial intervention group*

The pharmacy from the participating hospitals will provide bupivacaine with no adjuvants to the anesthesiologist prior to the start of surgery performing the block.

#### *6.1.1.3. Drug specified by Health Canada but is not a trial intervention drug*

The pharmacy from the participating hospitals will provide dexamethasone 2 mg to the anesthesiologist prior to the start of surgery.

### 6.1.2. Formulation, appearance, packaging and labelling

The medications are all commercially available formulations of the drugs.

### 6.1.3. Product storage and stability

Note that the interventional medications will be acquired by participants from the hospital pharmacy. Storage and stability as per product's label.

### 6.1.4. Preparation

Not applicable.

### 6.1.5. Dosing and administration

**PMC Group:**

- **Pregabalin**: **25** mg at night on the 5th day prior to surgery, 25 mg BID on the 4th day prior to surgery, 50 mg BID on the 3rd day prior to surgery, 75 mg BID on 2nd and 1st day **prior to surgery**. In our pilot data, 75 mg BID appeared effective and tolerated (Appendix VI). If participants do not tolerate the 75 mg dose (e.g. sedation), we will use the maximum tolerable dose.

**Non-steroidal anti-inflammatory drugs**: Celecoxib 100 mg PO BID starting 5 days **prior to surgery**. In case of contra-indication or intolerance, Naproxen EC 500 mg PO BID for 5 days will be used. For example, a sulfa allergy, or certain types of heart disease would be a reason to not prescribe celecoxib.

- 

**Block Group:**

- **Interscalene nerve block**. An anesthesiologist experienced in providing nerve blocks will administer a preoperative single shot interscalene peripheral nerve block, approximately 1 hour prior to the start of surgery. Bupivacaine will be primarily used for the peripheral anesthesia (Block). Adrenalized bupivacaine (containing epinephrine 5 µg/mL) in a volume of 5 to 15 mL, and a concentration of 0.5%, will be used. We will not use continuous interscalene block due to logistical challenges. Bupivacaine is indicated for the production of local or regional anesthesia and analgesia with the following procedures: local infiltration procedures, peripheral nerve blocks, retrobulbar blocks, caudal, epidural and subarachnoid (spinal) blocks. In this study it will be used to do an interscalene peripheral nerve block (Block).

#### *6.1.5.1. The timing of dosing and the relation of dosing to meals*

Pregabalin and Celecoxib or naproxen EC are prescription medications. Therefore, the research team will provide these instructions with the help of document checklists from the pharmacy. Bupivavaine will be administered approximately 1 hour prior to the start of surgery.

#### *6.1.5.2. Instructions to study participants about when or how to take the dose(s) should be described*

The pharmacy where these medications are filled will provide these instructions.

#### *6.1.5.3. Instructions or safety precautions for administration of the study agent.*

The research team with the help of document checklists from the pharmacy where pregabalin, celecoxib or naproxen EC are filled will provide instructions about product safety. The anesthesiologist performing the interscalene block will review the risks, benefits and expectations occur before a block is performed.

#### *6.1.5.4. Maximum hold time once thawed/mixed, if appropriate, before administration*

Not applicable.

#### *6.1.5.5. Describe the procedures for selecting each subject's dose of study agent and control product*

- **Pregabalin and Celecoxib**

The dosages of pregabalin and Celecoxib are based on the clinical experience of the site principal investigator Dr. Moreno Morelli who has used these medications for more than 10 years. His patients have found it effective in the management of POP with very little need for opioids compared to his practice prior to using these pre-emptive drugs (Appendix VI). If subject experiences any AE, they will be instructed to call the nurse, or QI who will suggest a reduced dose. This dose will be recorded in the subject's file.

- **bupivacaine**

The choice of dose for bupivacaine is based on the experience of the anesthesiologist, the physical size of the patient, and the visualization of drug deposition at the time of block performance under ultrasound guidance. To achieve local anesthetic nerve blockade, the drug must be deposited in and around the neural tissue that innervates the shoulder. This is accomplished with 5 to 15 mL of bupivacaine 0.5% with epinephrine 5 μg/mL in most subjects. The recommended dose for brachial plexus block (which includes an interscalene block) for adults is bupivacaine 0.5% with epinephrine 5 μg/mL not to exceed 30 mL.

### 6.1.6. Route of administration

Block: perineural.

PMC+Block: per os (p.o) + perineural.

### 6.1.7. Starting dose and dose escalation schedule

Starting dose and dose escalation schedule was described previously (Section 6.1.5).

### 6.1.8. Dose adjustments/modifications/delays

- **Pregabalin.** If subject experiences any AE, they will be instructed to call the nurse, or site PI/QI who will suggest a reduced dose. This dose will be recorded in the subject's file.

**Celecoxib or Naproxen EC.** Main concerns with anti-inflammatories would be stomach irritation or increase in blood pressure .

They will be instructed to discontinue the medication and be withdrawn from the study.

- **Bupivacaine**. Dose adjustment was described previously.

#### 6.1.9. Duration of therapy

The duration of the treatment period of the **planned trial interventions** is dependent on the study group:

- **Block**. The duration of the therapy for the Block intervention group is 1 day (anesthesia on day of surgery) (Day 6).
- **PMC+Block**. The duration is 6 days: 5 pre-operative therapy days, plus 1 day for the anesthesia at surgery (Days 1 to 6).

#### 6.1.10. Tracking of dose

**Before surgery**. For each participating hospital, an evaluator will monitor dosing and adherence to the planned pre-operative trial interventions by calling participants randomly allocated to the group PMC + Block on the appropriate days (Section 5.3.2).

**On the day of the surgery.** The evaluator will monitor participant's adherence to the planned treatment.

We will document challenges and the proposed solutions with all participating surgeons through internal communications. If we cannot increase adherence (defined as taking at least 50% of the medication as prescribed 5 days before surgery) to occur in at least 75% of participants, we will consider the definitive trial to be non-feasible.

#### 6.1.11. Device specific considerations

Not applicable.

### 6.2. Study Agent Accountability Procedures

Participants will acquire pregabalin and celecoxib (or naproxen) from the hospital pharmacy prior to the surgery, as prescribed by their surgeons. They will be responsible for the safekeeping of those medications after acquisition. The evaluator will instruct the participant to record the time/amount of pill used each day in the participant diary, and to bring the bottle of Rx and the diary on the day of surgery for accounting purposes.

All medications used during surgery (bupivacaine and dexamethasone) are provided by the hospital pharmacies and are part of standard procedure.

## 7. STUDY PROCEDURES AND SCHEDULE

### 7.1. Study Procedures/ Evaluations

#### 7.1.1. Study specific procedures that are not part of standard clinical care

The study procedures include:

- Screening (Days – 21 to 0) - see Sections 5.3.1 and 7.3.1
    - Medical history/prior medication. Evaluators will assess medical history and prior medication of the potential participants by calling them and from medical records, after potential participants sign the consent form. The objective is to ascertain the participant eligibility (Sections 5.1 and 5.2).
    - RAMQ The evaluators will assess RAMQ to ascertain the potential participant eligibility.
    - Blood test. A blood test will be required for all participants. It will be requested creatinine test to all patients who accept to participate in the study. These results will be provided to the potential participant.
- Enrolment/Baseline (Days -21 to 0) (Sections 5.3.1 and 7.3.1)
- Assessment of study agent adherence (Days 1, 3, 5) – (Section 5.3.2)
- Follow-up before surgery (Days 1, 3, 5, 12) – (Section 7.3.2)
- Follow-up on the day of surgery (Day 6) – (Section 7.3.2)
- Follow-up after surgery (Days 6, 7, 13, 66, 186) – (Section 7.3.2)
- Final study follow-up (Day 186) – (Section 7.3.2)
- Follow-up of the evaluators. Evaluators will complete the forms assessing the feasibility indicators – primary outcome (Table 2)
- End of enrolment data collection (when participating office has completed participant enrolment)
- Withdrawal from study – (Section 5.4)
- Unscheduled visit – (Section 7.3)
- Arrangements for day-to-day management of the trial

The lead Investigators (Drs. Velly and Morelli) and the methodologist co-investigator (Dr. Shrier) will supervise the site evaluator weekly who that will be responsible for the day-to-day management of the trial, contacting the evaluator to assess the study outcomes described in Section 4.2.1 and Tables 2- 3.

#### 7.1.2. Standard of care procedures

All participants undergoing arthroscopic surgery for shoulder rotator cuff pathology or shoulder instability **will receive a general anesthetic, as well as a** standardized approach to pain management. The provision of intraoperative analgesia will include titrated opioid as required.

In addition, all participants will receive **dexamethasone 2 mg** and ondansetron (4 mg), unless contraindicated through the interscalene block and intravenously respectively. Dexamethasone is a steroid, that will be used in this study to standardize the provision of anesthesia and the treatment of side effects secondary to general anesthesia (**GA**). Nausea and/or vomiting occur in approximately 30% of patients after GA. This is problematic in this ambulatory surgical population. Most ambulatory patients are treated prophylactically for PONV with single doses of ondansetron and dexamethasone. Ondansetron is "on label" and Dexamethasone is "off label" for PONV; however, the Society for Ambulatory Anesthesia guidelines (2007) makes

recommendations for their use in the described doses (69). Studies demonstrate that single dose intravenous dexamethasone can result in improved pain management and prolongation of peripheral nerve block (58,59). Both of the outcomes can have an impact on this study.

As such, by standardizing its use, we expect a reduction in study confounders. Dexmedetomidine, magnesium and intravenous lidocaine (exceeding 100 mg) will be avoided as they may contribute to the POP experience.

On the morning of surgery, **all participants will begin the same standardized pain management approach** that consists of:

- Pregabalin initiated at a dose of 75 mg BID for 6 days (including the day of surgery), followed by a step-down dose of 50 mg BID for 2 days and subsequently 25 mg BID for 2 days;
- Celecoxib 100 mg BID continued through postoperative day 5; and
- Tramadol one-tab q 6h and Acetaminophen 500mg q 6h PRN (or as needed) continued through postoperative day 10 regularly Breakthrough pain experienced in the post-anesthetic care unit will be managed as needed with an intravenous opioid;
- Participants will be provided intravenous fentanyl or hydromorphone in the post-anesthetic care unit, as directed by the subject's anesthesiologist if rescue analgesia is required. For subjects experiencing post-operative nausea/vomiting, a second dose of ondansetron will be provided. A third-line medication (dimenhydrinate) can also be provided.

## 7.2. Laboratory Procedures/ Evaluation

### 7.2.1. Standard of care procedures

It will be requested that participants take a blood test. It will be requested creatinine test to all patient who accept participate in the study.

### 7.2.2. Other assays or procedures

Because hyperkalemia and renal impairment are exclusion criteria, serum electrolytes and serum creatinine values are required.

In these hospitals, all females under age 55 get pregnancy test prior to surgery. If they are pregnant, surgery gets cancelled. This is not a procedure specific for this study, but a standard practice in all hospitals before surgery.

### 7.2.3. Specimen preparation, handling and storage

Not applicable.

### 7.2.4. Specimen shipment

Not applicable.

## 7.3. Study Schedule

The procedures listed below are consistent with those included in the Study Schedule (Appendix VII).

### 7.3.1. Screening, enrolment and baseline (Day -21 to 0)

- **Screening**

Patients who are planning to undergo arthroscopic surgery for shoulder rotator cuff pathology or shoulder instability at the enrolled orthopedic clinics (e.g., St. Mary's Hospital Montreal, Quebec), will be screened for possible participation in this study. The evaluators will ask the potential participants to read the consent form and will answer any questions they may have before choosing to sign the consent form. The evaluators will execute the consent process according to IRB requirements. Once potential participants give consent by signing the form, the evaluators will review the inclusion/exclusion criteria to determine if the patient meets eligibility criteria for the trial (see Section 5.2 Exclusion Criteria). The procedures to contact the potential participants and screen them are described in Section 5.3.1.

- **Enrolment**
  - Randomization

After a participant has provided consent and their eligibility is confirmed, the participant's random assignment to PMC + Block or Block is automatically available to the evaluators on the tablet. The randomization table of assignments will be provided by DACIMA before recruitment starts. The participating subjects will then be informed of their group assignment.

  - Baseline assessment

A blinded evaluator will collect baseline information, asking the participants to complete the POQ (67,68) to assess baseline pain intensity, disability, and impact of pain on sleep, walking, work and mood. Patient Health Questionnaire-4 (70,71) will be used to assess the overall measure of emotional burden (anxiety, depression symptoms). Previous treatment(s), gender, height, and weight will also be recorded at that time. If an enrolled patient declines to provide any of the baseline data, this decision will be considered a voluntary withdrawal from the study (Retention strategy is described in Section 5.3.2).

The evaluators will call participants randomized to PMC+Block intervention groups seven days before PMC onset to remind them to initiate their medication 5 days before surgery (Section 5.3.2), and to complete the participant diary (D1 to 5) that will be used to assess the concomitant medications and AE.

### 7.3.2. Follow-up

- **Before Surgery** (Days 1-5)

- ***Study days 1, 3 and 5***
  - Evaluators will call participants allocated to the group PMC + Block on study days 1, 3, and 5 to monitor dosing, adherence to the planned trial interventions as well as AE.
  - Another evaluator blinded to group assignment will call participants to assess pain intensity using the POQ (67,68).
  - The evaluator will call participants to remind them to take the required medication before surgery (seven days before PMC onset).

- **Surgery** (Day 6)
  - **Adherence**. On the day of surgery, the evaluators will assess the patient's adherence to the planned treatment as well as the AE (Section 5.3.2).

- **Follow-up 6 hrs (Day 6), 1 day (Day 7), 1 week (Day 13), and 2 months (Day 66) after surgery**
  - An evaluator blinded to group assignment will call participants 6 hrs, 1 day, 1 week and 2 months after surgery to assess pain intensity with the POQ (67,68). At 2 months after surgery, evaluators will also assess physical activity with the self-assessment portion of the POQ.
  - A different evaluator (not involved in pain assessment), will call participants to assess AE and if they received **opioid and non-opioid supplemental pain management** (rescue medication, other treatments).
  - Participants will complete the participant diary (PD) before and after surgery to assess the use of their PMC medication, concomitant medications, and AE.

#### 7.3.3. Final study visit (Day 186)

- An evaluator blinded to group assignment will call participants to assess pain intensity and physical activity using POQ at **6 months post-surgery**.
- **Another** evaluator will call to assess the use of opioid and non-opioid supplemental pain management, and review AE.

#### 7.3.4. Early termination visit

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to determination of unexpected, significant, or unacceptable risk to participants.

The data collection authorized will be the record date of the early termination, reason for withdrawal, information needed to address an unanticipated problem, and safety issues that may have led to the patient's withdrawal from the study.

#### 7.3.5. Unscheduled visit

For the purpose of the study, the participating patient does not need to see the surgeon after surgery. However, s/he may return to the surgeon with concerns after the surgery. If surgeon cannot determine if the concern is related to the pilot RCT or believes it is related to the study, then s/he will inform the site PI/QI and the evaluator who will discuss this event with the PI. If surgeons deem the event to be an AE, then it will be reported as described in (Section 8.4).

#### 7.3.6. Schedule of events

Appendix VII lists the schedule of events and assessments.

### 7.4. Concomitant Medications, Treatments, and Procedures

Potential concomitant medications provided during surgery are dexamethasone and ondansetron.

### 7.5. Justification for Sensitive Procedures

N/A.

### 7.6. Prohibit Medications, Treatments, and Procedures

For precautionary statement with concomitant medications please refer to Product Monograph: Section Drug Interactions. There are no specifically prohibited medications and the interpretation of the monograph is left to the discretion of the PIs.

### 7.7. Prophylactic Medications, Treatments, and Procedures

Not applicable.

### 7.8. Rescue Medications, Treatments, and Procedures

Participants will be provided intravenous fentanyl or hydromorphone in the post-anesthetic care unit, as directed by the subject's anesthesiologist if rescue analgesia is required. Tramadol one-tab q 6h and Acetaminophen 500mg q 6h will be continued through postoperative day 10 regularly, when needed. Concomitant medications, if used, will be recorded in the Participant diary.

### 7.9. Participation Access to Study Agent at Study Closure

Not applicable.

# 8. ASSESSMENT OF SAFETY

## 8.1. Specification of Safety Parameters

Safety monitoring for this study will focus on the assessment of AE, serious adverse events (SAE), and unanticipated problems (UP) during all the study.

### 8.1.1. Adverse events (AE) and adverse drug reaction (ADR)

An AE is defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment." "An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product"(72).

An adverse drug reaction (ADR) is any noxious and unintended response to a medicinal product related to any dose. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and the AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

### 8.1.2. Serious adverse events (SAE)

In accordance with the ICH E2A guideline, a serious adverse event (SAE) or reaction (SDR) is "*any untoward medical occurrence that at any dose":*

- Results in death
- Is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation or results in prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above."

### 8.1.3. Unexpected adverse reaction (UP)

In accordance with the ICH E2A guideline an unexpected adverse reaction (UP) is defined when an "the nature, or severity of the AE is not consistent with the applicable product information

(e.g. Investigator's Brochure for any approved investigational medicinal product, Product Monograph for marketed product)." "An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labeling specifically states that the ADR might be associated with a fatal outcome".

There are other types of incidents and outcomes that are not considered AEs, but are considered as unanticipated problems (e.g., breach of confidentiality or other incidents involving social or economic harm).

## 8.2. Classification of an Adverse Event

### 8.2.1. Severity of event

The investigator will evaluate the severity of each AE using the following grade consistent with the CTCAE's definition:

- **Mild:** Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the patient's overall health and well-being, does not interfere with the patient's usual function, and is not likely to require medical attention.
- **Moderate:** Sign or symptom causes interferences with the usual activity or affect clinical status and may require medical intervention.
- **Severe:** Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
- **Life-threatening:** Sign or symptom results in a potential threat to life.
- **Fatal:** Sign or symptom results in death.

### 8.2.2. Relationship to study agent

To assess the relationship of an event to study intervention, the following guidelines are used:

- Related (Possible, Probable, Definite)
    - The event is known to occur with the study intervention
    - There is a temporal relationship between the intervention and event onset
    - The event decreases when the intervention is discontinued
    - The event reappears upon a re-challenge with the intervention
- Not Related (Unlikely, Not Related)
    - There is no temporal relationship between the intervention and event onset
    - An alternate etiology has been established

#### 8.2.3. Expectedness of severe adverse events

The site PI/QI and lead PI will be responsible for determining whether an SAE is expected or unexpected.

## 8.3. Time Period and Frequency for Event Assessment and Follow-up

AE, SAE, and UPs will be identified during the study. This assessment will be made by the evaluator during the calls and during the scheduled orthopedic clinic visit (2 and 6 months). The investigator will treat the subject as medically required until the AE either resolves or becomes medically stable. Subsequent follow-up after 6 months period will depend on its severity. As happens with health care systems in Canada, referral to specialist can be initiated by the orthopedic surgeon from each site (see Table 1).

Patients who experience SAEs, or AEs that are ongoing at end of study and possibly related to the study medication, will be followed-up by telephone for up to 42 days after the last dose study medication to assess their outcome. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histo-pathological examinations, or consultation with other health care professionals.

Should one of these events require more urgent assessment and treatment, participants can seek treatment through an emergency department visit or call back to the most responsible physician (the orthopedic surgeon). Should referral to a subspecialist be required. The most responsible physician can make this referral.

## 8.4. Reporting Procedures

#### 8.4.1. Serious adverse event reporting

This protocol will be filed under a Clinical Trial Application (CTA) with the TPD of Health Canada. A given SAE may require submitting a CTA Safety Report if the SAE is attributable to the study drug and is unexpected. When a site receives an Initial or Follow-up CTA Safety Report or other safety information from the Coordinating Investigator (Sponsor), the investigator or designee is required to promptly notify his or her IRB.

#### 8.4.2. Unanticipated problem reporting

Incidents or events that meet the unanticipated problems will be reported to IRB. The report will include the following information:

- Title and number of the protocol, IRB project number and investigator's names;
- Patient details;
- A description of the unanticipated problems;
- Details of the AE, incident, experience, or outcome represents an unanticipated problem;

- Suspected medicinal product;
- Outcome

A description of any change to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

Table shows the timeline for prompt reporting of an unanticipated problems.

| Table 4. Reporting timeline | |
|---|---|
| **Fatal or life-threatening** unexpected ADRs qualify for very rapid reporting | Regulatory agencies should be notified (e.g., by telephone, fax, or in writing) as soon as possible but **no later than 7 calendar days** after first knowledge that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. |
| Serious, unexpected reactions that are **not fatal or life-threatening** | Must be filed as soon as possible but **no later than 15 calendar** days after first knowledge by the lead PI that the case meets the minimum criteria for expedited reporting. |
| All unanticipated problems | Will be reported to appropriate institutional officials within one month of the IRB's receipt of the report of the problem from the investigator. |

#### 8.4.3. Events of special interest

Not applicable.

#### 8.4.4. Reporting of pregnancy

Participants reporting pregnancy during the study will be withdrawn. This will be reported to the IRB from the hospital where the patient was recruited.

### 8.5. Study Halting Rules

The evaluator will track and record all AEs, SAE and UP throughout the trial. Decisions about stopping the trial will be made either by the PI and site PI/QI. The investigators can stop enrollment in the study at any time based on the occurrence of an AE, SAE or UP that they deem of sufficient concern.

### 8.6. Safety Oversight

The Lead PIs, site PI/QI and epidemiologist (Dr. Shrier) reviewed this clinical trial based upon the trial study design described in the grant application.

## 9. CLINICAL MONITORING

The Lead Investigators (Drs. Velly and Morelli), the site PI/QI, the Epidemiologist (Dr. Shrier), the research coordinator and the site evaluator will oversee the progress of the trial to ensure that the trial is being conducted in accordance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirement(s), and is in adherence to human subject protections, including completeness of consenting procedures and accuracy of data collection.

A **written report** of this meeting will be prepared by the research coordinator. This report will include a summary of what the site evaluator reviewed and any statements concerning the significant findings, deviations and deficiencies, actions taken or to be taken and/or actions recommended to secure compliance. This report will include the date, site, name of the research coordinator (monitor), and name of the Lead Investigators, the site PI/QI, the Epidemiologist, the research coordinator, and the site evaluator.

The regulatory agency, the IRB from each hospital participant reserves the right to perform the audits as necessary. Clinical site monitoring will not be conducted.

# 10. STATISTICAL CONSIDERATIONS

## 10.1. Statistical and Analytical Plans

Summary descriptive statistics and thresholds of acceptability for each feasibility criterion for recruitment, blinding, adherence, dropout, response rates, and time needed to collect data will be provided.

## 10.2. Statistical Hypotheses

This pilot RCT does not test a hypothesis**.**

## 10.3. Analysis Datasets

### 10.3.1. Analysis of the primary efficacy endpoints

We will describe feasibility criteria with simple summary statistics and thresholds of acceptability for each criterion as follows: ≥30% for recruitment, % blinding (no threshold), adherence by ≥ 75% of participants, ≤20% for dropout, ≥80% for response rates, and ≤ 25% time needed to collect data. We will report the mean, median and range of time to collect data, for which we do not have a fixed threshold of acceptability. We will ask the participants their impressions about what length would be acceptable. If more than 25% of participants consider the time unacceptable, the definitive RCT will focus on the most important data. For our variance estimation, we will report proportions with 95%CI for each group for dichotomous measures, the mean with SD for each group for continuous measures, and the intra-class correlation coefficients.

### 10.3.2. Safety analysis

A description and frequency of each AE, SAE and UP, as a proportion with 95%CI for each group will be calculated.

### 10.3.3. Baseline descriptive analysis

Descriptive statistics will be used for baseline variables.

### 10.3.4. Planned interim analysis

No interim analyses are planned.

## 10.4. Determination of Sample Size

For this pilot RCT, we did not perform any power analysis to estimate the sufficient sample size. We will recruit a total of 36 participants, 12 from each of three institutions. This sample size will provide enough information to identify major challenges for the feasibility of a definitive future RCT.

Our proposed pilot RCT will allow us to better estimate the sample size for the future large definitive trial because: (i) the pilot study will be a RCT with a much lower risk of bias; and (ii) 18 subjects per group will provide relatively stable estimates of variance for our continuous measures for each institution. We will estimate intra- and inter-hospital variation of the outcome measures to further improve sample size calculation precision.

## 10.5. Measures to Minimize Bias

### 10.5.1. Enrollment/randomization

After a patient has provided consent and their eligibility is confirmed, the patient's random assignment to PMC + Block or Block is automatically available to the evaluators on the tablet.

DACIMA Software, Inc will develop and run a computer program to randomize participants using random number generation stratified by surgeon. We have stratified by surgeon because there is always variation in surgical technique between surgeons. The sequence will use randomized blocks of size 3 or 6, in each of which both treatments are evenly present.

After consent is obtained and the participant's eligibility is confirmed, the evaluator will inform the participant of his/her randomly assigned treatment. The randomization table of assignments will be provided by DACIMA before recruitment starts. The evaluator will inform the doctor of the assigned treatment. The anesthesia department has agreed to arrange their scheduling so that one of these anesthesiologists will be available to perform the block when the need arises.

### 10.5.2. Evaluation of success of blinding

The site evaluator who will assess pain intensity during the study will be blinded to the group allocation. It is not possible to blind the anesthesiologists, surgeons or participants because the effectiveness of the block is evaluated by asking the patient if they have numbness in the regions supplied by the nerves being blocked. Also, it will be difficult to blind the evaluator who will assess pain management as well as the AE during the study. We will blind the statistician supervising the analyses because it is feasible and reduces the risk of certain biases (e.g., detection bias). Further, we will ask participants not to disclose their treatment to the site evaluators.

We will assess the success of blinding by asking the evaluators to guess the participants' study group and the supporting reasons (to determine if unblinding was caused by the active treatment efficacy or AE) (64,76,77).

### 10.5.3. Breaking the study blind/participation code

Only the study statistician and the evaluator assessing pain intensity will be blinded as described in Section 10.5.2.

## 11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating hospital will maintain appropriate medical and research data/documents for this study, in compliance with *Section 8* of the *ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial)* (78) and regulatory and institutional requirements for the protection of confidentiality of subjects.

Study staff will permit authorized representatives of the IRB of the participant hospital to examine (and copy when required by applicable law) research records for the purposes of audits, evaluation of the study safety, quality assurance reviews, and data validity.

## 12. QUALITY ASSURANCE AND QUALITY CONTROL

Data collection will occur using the DACIMA Clinical Suite electronic data capture (EDC) system that employs on-screen data validation and alerts. The forms will be evaluated by the study team prior to the development of the electronic data capture system, and the system will be tested and validated prior to the study launch.

The study team will develop a data management plan with quality management procedures including the development of data quality checks and processes related to quality review and management of data entered. DACIMA will be responsible for developing and maintaining the database software including developing the electronic Case Report Forms (eCRFs), editing checks and configuring the study database. Authorized study personnel will be responsible for validating the data, and locking and closing the database. The research nurse and assistant will both be trained on the system prior to patient enrollment. All records will be kept for 15 years after the completion of the study. No records will be destroyed without the written consent of the sponsor.

# 13. ETHICS/PROTECTION OF HUMAN SUBJECTS

## 13.1. Ethical Standard

The Lead investigator will ensure that this trial is conducted in full conformity with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

## 13.2. Institution Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB at each hospital participating in this study for review and approval. Approval of both the protocol and the consent form must be obtained before any patient is enrolled. Any amendment to the protocol will require review and approval by the regulatory agency and IRB before the changes are implemented in the study.

## 13.3. Informed Consent Process

### 13.3.1. Consent/Assent and other information documents provided to participants

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. The consent form will describe in detail the study procedures and risks. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

### 13.3.2. Consent procedures and documentation

The potential participant is required to read and review the document. In addition, the evaluators will explain the research study to the potential patient and answer any questions that may arise. Potential participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate.

The potential participant will sign the informed consent document prior to any study-related assessments or procedures. Participants may withdraw consent at any time throughout the course of the trial.

A consent form approved by the IRB will be given to the participant and other copies will be kept in the office of the site PI/QI Dr. Morelli). The consent process will be documented in the research record.

### 13.4. Exclusion of Women, Minorities, and Children (Special Populations)

Individuals of any sex or racial/ethnic group may participate in the trial. Children will be excluded.

### 13.5. Participation and Data Confidentiality

The study protocol, documentation, data, and all other information from the trial will be held in strict confidence. No information concerning the trial or the data will be released to any unauthorized third party without prior written approval of the Lead PIs (Drs. Velly and Morelli).

The evaluators, site PI/QI, Lead PIs or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained, including but not limited to, medical records (from the clinic, or hospital) of the study participants. The clinical study site will permit access to such records.

The security features of the data capture system will enforce strict limits on data access for various members on the team. The system will be configured to give study personnel "minimum necessary" access to data given the role of the person in the project.

To further protect the privacy of study participants, the National Institute of Health (**NIH**) has updated a policy for issuing Certificates of Confidentiality. This certificate allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceedings, whether at the federal, provincial, or local level. The aim is to protect identifiable research information from forced disclosure. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to subjects.

### 13.6. Future Use of Stored Specimens

Not-applicable.

# 14. DATA HANDLING AND RECORD KEEPING

The study team is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs) and source documentation.

Only study personnel (i.e., Lead PIs, site PI/QIs, co-investigators, study coordinator, and evaluators) will have access to the study data elements in the study database.

## 14.1. Data Collection and Management Responsibilities

Data collection and any other necessary document collected during study are the responsibility of the site evaluator under the supervision of the Lead PIs and site PI/QI. All source documents must be reviewed by the study team, who will ensure that they are accurate and complete.

Consent forms, questionnaires completed by participants will be kept at the office of each site. A copy of the consent form will be kept in PI office.

DACIMA will provide support and processes to allow for accuracy and completeness of data collected. AE, SAE and UP must be recorded by the evaluators, and reviewed by the evaluators, site PI/QI and Lead PIs.

DACIMA will be responsible for developing, monitoring, maintaining, locking, and closing databases. DACIMA will conduct quality control and quality assurance measures to evaluate and maintain study data quality. Evaluators, study coordinator, site PI/QI and PIs will be trained on the EDC system by DACIMA staff.

### 14.1.1. Data capture methods

This study will utilize a centralized electronic data capture (EDC) system, developed and maintained by the DACIMA, for the evaluator to enter data into web-based CRFs. The EDC system employs on-screen data validation utilizing univariate and multivariate alerts, as needed, including valid-value, valid-range, and missing-value alerts. These validations will prevent users from continuing with study data collection if invalid or missing data entries are provided.

The EDC system provides comprehensive and extensible support for both Authentication and Authorization through role-based access control. Access to the EDC system will be available to specific study team members, site study staff, and DACIMA study staff. Staff eligible to access the web application will be assigned an application-specific user account and will create a unique password to access the application. All access to the systems is based on authorization by the PI and/or the DACIMA manager or their delegates. Access to sections within the EDC application will be role-based, thereby limiting the user's access only to pertinent information for their role with participants at their assigned study site.

Data collected on CRFs through the DACIMA application is transmitted to and stored in the EDC system essentially in real time. Only key study and DACIMA staff will have direct access to the core EDC system and its data. Therefore, each user of the EDC system is permitted access to only the minimum necessary data required to fulfill their role in the study.

#### 14.1.2. Types of data

Data collected is shown in Appendix VII. A description of when these instruments will be used is found in Sections 4.2 and 7.3.2.

#### 14.1.3. Schedule and content of reports

The site evaluators will provide reports of the feasibility indicators (recruitment and consent, treatment allocation randomization, adherence and dropouts), as well as reports on pain intensity, AE, SAE, and UP to the research coordinator, Lead PIs (Drs. Velly and Morelli), site PI/QI, and epidemiologist (IS). The reports will be produced every two weeks until the 7-day follow-up is closed, and every month until the 6-month follow-up is completed. Reports on participants who dropout will be issued after data have been obtained.

### 14.2. Study Records Retention

All records will be kept for 15 years after the completion of the study. No records will be destroyed without the written consent of the lead PIs (Drs. Velly and Morelli) and site PI/QIs, if applicable. It is the responsibility of the lead PI and site PI/QIs to inform when these documents no longer need to be retained. Each site will comply with the local requirements for data retention and destruction.

### 14.3. Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol and Good Clinical Practice. Therefore, failure to comply with any interventions for the participant group would be a protocol deviation. The noncompliance may be also on the part of the investigator or evaluators. A s a result of deviations, corrective actions may be developed by the study staff and should be implemented promptly. Table describes the investigators and sponsor obligations as described in ICH E6.

**Table 5. Obligations as described in ICH E6**

| Sections | ICH E6 |
|---|---|
| 4.5.1 | The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement. |

| Table 5. Obligations as described in ICH E6 | |
|---|---|
| 4.5.2 | The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)). |
| 4.5.3 | The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol. |
| 4.5.4 | The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to: a) the IRB/IEC for review and approval/favourable opinion; b) the sponsor for agreement and, if required; c) the regulatory authority(ies). |
| 5.1.1 | The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). |
| 5.20.1 | Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance. |
| 5.20.2 | If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the participation of the investigator/institution in the trial. When the participation of an investigator/institution is terminated because of noncompliance, the sponsor should promptly notify the regulatory authority(ies). |

All deviations from the protocol must be addressed in the source documents for the study participant and reported to the local IRB(s), according to their requirements. Deviations must also be reported to CIHR at the timeframe for which the deviations are reported to the local IRB(s).

### 14.4. Publication and Data Sharing Policy

This study will comply with the CIHR Public Access Policy, which ensures that the public has access to the published results of CIHR funded research. Therefore, we will submit final peer-reviewed journal manuscripts to the digital archive PubMed Central upon acceptance for publication. This pilot RCT will be registered in a public trials' registry (ClinicalTrials.gov).

# 15. STUDY ADMINISTRATION

## 15.1. Study Leadership

Dr. Velly and Dr. Morelli, (Lead Investigators) are responsible for overseeing the study.

**16.** The Qualified Investigator is Dr. Moreno Morelli (St. Mary's Hospital)

# 17. CONFLICT OF INTEREST POLICY

Any conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this pilot RCT will be disclosed and managed. Persons who have a perceived conflict of interest will be required to have such conflicts managed in way that is appropriate to their participation in the trial.

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## 19. APPENDICES

## 19.1. Appendix I: Pregabalin Adverse Events

Table 1. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled Studies in neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at Least 2% of Participants Receiving Pregabalin and More Frequent Than in Placebo Treated Participants).

| Body System Preferred Term | Placebo (N = 459) % | Pregabalin (mg/day) | | | |
|---|---|---|---|---|---|
| | | 75 (N =77) % | 150 (N =212) % | 300 (N = 321) % | 600 (N = 369) % |
| **Body as a whole** | | | | | |
| Infection | 6.1 | 3.9 | 7.5 | 8.4 | 4.6 |
| Asthenia | 2.4 | 3.9 | 1.9 | 4.4 | 7.3 |
| Pain | 3.9 | 5.2 | 4.2 | 2.5 | 4.9 |
| Accidental injury | 2.8 | 5.2 | 2.4 | 2.2 | 5.7 |
| Back pain | 0.4 | 0.0 | 2.4 | 1.2 | 1.9 |
| Chest pain | 1.1 | 3.9 | 1.4 | 1.2 | 1.6 |
| Face edema | 0.4 | 0.0 | 0.9 | 0.9 | 2.2 |
| **Digestive system** | | | | | |
| Dry mouth | 1.1 | 2.6 | 1.9 | 4.7 | 6.5 |
| Constipation | 1.5 | 0.0 | 2.4 | 3.7 | 6.0 |
| Diarrhea | 4.8 | 5.2 | 2.8 | 1.9 | 3.0 |
| Flatulence | 1.3 | 2.6 | 0 | 2.2 | 2.7 |
| Vomiting | 1.5 | 1.3 | 0.9 | 2.2 | 1.1 |
| **Hemic and lymphatic system** | | | | | |
| Ecchymosis | 0.2 | 2.6 | 0.5 | 0.6 | 0.3 |
| **Metabolic and nutritional disorders** | | | | | |
| Peripheral edema | 2.4 | 3.9 | 6.1 | 9.3 | 12.5 |
| Weight gain | 0.4 | 0.0 | 4.2 | 3.7 | 6.2 |
| Edema | 0.0 | 0.0 | 1.9 | 4.0 | 1.9 |
| Hypoglycemia | 1.1 | 1.3 | 3.3 | 1.6 | 1.1 |

Table 1. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled Studies in neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at Least 2% of Participants Receiving Pregabalin and More Frequent Than in Placebo Treated Participants).

| Body System Preferred Term | Placebo (N = 459) % | Pregabalin (mg/day) | | | |
|---|---|---|---|---|---|
| | | 75 (N =77) % | 150 (N =212) % | 300 (N = 321) % | 600 (N = 369) % |
| **Nervous system** | | | | | |
| Dizziness | 4.6 | 7.8 | 9.0 | 23.1 | 29.0 |
| Somnolence | 2.6 | 3.9 | 6.1 | 13.1 | 16.3 |
| Neuropathy | 3.5 | 9.1 | 1.9 | 2.2 | 5.4 |
| Ataxia | 1.3 | 6.5 | 0.9 | 2.2 | 4.3 |
| Vertigo | 1.1 | 1.3 | 1.9 | 2.5 | 3.5 |
| Confusion | 0.7 | 0.0 | 1.4 | 2.2 | 3.3 |
| Euphoria | 0.0 | 0.0 | 0.5 | 3.4 | 1.6 |
| Thinking abnormal | 0.0 | 1.3 | 0.0 | 0.9 | 3.0 |
| Abnormal gait | 0.0 | 1.3 | 0.0 | 0.6 | 2.7 |
| Reflexes decreased | 1.7 | 3.9 | 0.5 | 1.2 | 1.4 |
| Amnesia | 0.2 | 2.6 | 0.9 | 0.0 | 2.2 |
| Hypesthesia | 0.7 | 2.6 | 0.0 | 0.0 | 0.8 |
| Hyperalgesia | 0.2 | 2.6 | 0.0 | 0.0 | 0.3 |
| **Respiratory system** | | | | | |
| Dyspnea | 0.7 | 2.6 | 0.0 | 1.9 | 1.9 |
| **Skin and appendages** | | | | | |
| Pruritus | 1.3 | 2.6 | 0.0 | 0.9 | 0.0 |
| **Special senses** | | | | | |
| Blurred vision[b] | 1.5 | 2.6 | 1.4 | 2.8 | 5.7 |
| Conjunctivitis | 0.2 | 2.6 | 1.4 | 0.6 | 0.3 |

Table 2. Adverse Events Most Frequently (≥2% of patients) Leading to Discontinuation in Placebo-Controlled Studies in Patients with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

| COSTART Preferred Term | Placebo (N = 459) % | Pregabalin (mg/day) | | | |
|---|---|---|---|---|---|
| | | 75 (N =77) % | 150 (N = 212) % | 300 (N = 321) % | 600 (N = 369) % |
| Dizziness | 0.4 | 0.0 | 1.4 | 1.9 | 5.7 |
| Somnolence | 0.0 | 0.0 | 0.0 | 1.6 | 4.1 |

Table 3. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

| Body System Preferred Term | Placebo (N = 398) % | Pregabalin (mg/day) | | | |
|---|---|---|---|---|---|
| | | 75 (N =84) % | 150 (N = 302) % | 300 (N = 312) % | 600 (N = 154) % |
| **Body as a whole** | | | | | |
| Infection | 3.5 | 14.3 | 8.3 | 6.4 | 2.6 |
| Headache | 5.3 | 4.8 | 8.9 | 4.5 | 8.4 |
| Pain | 3.8 | 4.8 | 4.3 | 5.4 | 4.5 |
| Asthenia | 4.0 | 3.6 | 5.0 | 2.6 | 5.2 |
| Accidental injury | 1.5 | 3.6 | 2.6 | 3.2 | 5.2 |
| Flu syndrome | 1.3 | 1.2 | 1.7 | 2.2 | 1.3 |
| Face edema | 0.8 | 0.0 | 1.7 | 1.3 | 3.2 |
| Malaise | 1.0 | 2.4 | 0.3 | 0.6 | 0.0 |
| **Cardiovascular system** | | | | | |
| Vasodilatation | 1.3 | 2.4 | 1.0 | 0.6 | 0.0 |
| **Digestive system** | | | | | |
| Dry mouth | 2.8 | 7.1 | 7.0 | 6.1 | 14.9 |
| Constipation | 2.3 | 3.6 | 4.6 | 5.4 | 5.2 |
| Diarrhea | 4.0 | 2.4 | 4.3 | 3.5 | 4.5 |

| | | | | | |
|---|---|---|---|---|---|
| Flatulence | 1.0 | 2.4 | 1.3 | 1.6 | 3.2 |
| Vomiting | 0.8 | 1.2 | 0.7 | 2.9 | 2.6 |
| **Metabolic and nutritional disorders** | | | | | |
| Peripheral edema | 3.5 | 0.0 | 7.9 | 15.7 | 16.2 |
| Weight gain | 0.3 | 1.2 | 1.7 | 5.4 | 6.5 |
| Edema | 1.3 | 0.0 | 1.0 | 2.2 | 5.8 |
| Hyperglycemia | 0.8 | 2.4 | 0.3 | 0.0 | 0.0 |
| **Nervous system** | | | | | |
| Dizziness | 9.3 | 10.7 | 17.9 | 31.4 | 37.0 |
| Somnolence | 5.3 | 8.3 | 12.3 | 17.9 | 24.7 |
| Ataxia | 0.5 | 1.2 | 2.0 | 5.4 | 9.1 |
| Abnormal gait | 0.5 | 0.0 | 2.0 | 3.8 | 7.8 |
| Confusion | 0.3 | 1.2 | 2.3 | 2.9 | 6.5 |
| Thinking abnormal[a] | 1.5 | 0.0 | 1.7 | 1.3 | 5.8 |
| Incoordination | 0.0 | 2.4 | 1.7 | 1.3 | 2.6 |
| Amnesia | 0.0 | 0.0 | 1.0 | 1.3 | 3.9 |
| Speech disorder | 0.0 | 0.0 | 0.3 | 1.3 | 3.2 |
| Insomnia | 1.8 | 0.0 | 0.7 | 2.2 | 0.0 |
| Euphoria | 0.0 | 2.4 | 0.0 | 1.3 | 1.3 |
| Nervousness | 0.5 | 0.0 | 1.0 | 0.3 | 2.6 |
| Tremor | 1.5 | 1.2 | 0.0 | 1.0 | 2.6 |
| Hallucinations | 0.0 | 0.0 | 0.3 | 0.3 | 3.2 |
| Hyperesthesia | 0.3 | 2.4 | 0.3 | 0.0 | 1.3 |
| **Respiratory system** | | | | | |
| Bronchitis | 0.8 | 0.0 | 1.3 | 1.0 | 2.6 |
| Pharyngitis | 0.8 | 0.0 | 2.6 | 0.6 | 0.6 |
| Rhinitis | 1.8 | 1.2 | 0.7 | 0.6 | 3.2 |

| | | | | | |
|---|---|---|---|---|---|
| **Skin and appendages** | | | | | |
| Rash | 3.0 | 2.4 | 2.0 | 2.9 | 5.2 |
| **Special senses** | | | | | |
| Blurred vision[b] | 2.5 | 1.2 | 5.0 | 5.1 | 9.1 |
| Diplopia | 0.0 | 0.0 | 1.7 | 1.9 | 3.9 |
| Abnormal vision | 0.3 | 0.0 | 1.0 | 1.6 | 5.2 |
| **Urogenital system** | | | | | |
| Urinary tract infection | 1.5 | 0.0 | 2.3 | 1.6 | 3.2 |

Table 4. Adverse Events Most Frequently (2% of patients) Leading to Discontinuation in Placebo-Controlled Studies in Patients with Neuropathic Pain Associated with Postherpetic Neuralgia

| **Number (%) of Patients** | | | | | |
|---|---|---|---|---|---|
| **Preferred Term** | Placebo (N = 398) % | **Pregabalin (mg/day)** | | | |
| | | 75 (N =84) % | 150 (N = 302) % | 300 (N = 312) % | 600 (N = 154) % |
| Dizziness | 0.8 | 0.0 | 3.6 | 3.8 | 7.8 |
| Somnolence | 0.3 | 0.0 | 2.0 | 3.8 | 6.5 |
| Confusion | 0.3 | 0.0 | 0.7 | 1.6 | 5.2 |
| Peripheral edema | 0.3 | 0.0 | 0.7 | 1.6 | 3.2 |
| Ataxia | 0.0 | 0.0 | 0.3 | 1.6 | 2.6 |
| Abnormal gait | 0.0 | 0.0 | 0.0 | 1.3 | 2.6 |
| Hallucinations | 0.0 | 0.0 | 0.0 | 0.3 | 2.6 |
| Dry mouth | 0.3 | 0.0 | 0.0 | 0.0 | 2.6 |

**Table 5.** Incidence (%) of Treatment-Emergent Adverse Events in a Placebo-Controlled Study in Neuropathic Pain Associated with Spinal Cord Injury (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

| **Body System Preferred Term** | **Placebo** | **Pregabalin 150 - 600 mg/day)** |
|---|---|---|
| | N = 67 | N = 70 |
| | % | % |
| **Body as a whole** | | |
| Asthenia | 6.0 | 15.7 |
| Infection | 6.0 | 8.6 |
| Abdomen enlarged | 0.0 | 4.3 |
| Pain | 1.5 | 4.3 |
| Back pain | 1.5 | 2.9 |
| Cellulitis | 0.0 | 2.9 |
| Flu syndrome | 1.5 | 2.9 |
| Neck pain | 1.5 | 2.9 |
| **Cardiovascular system** | | |
| Hypotension | 0.0 | 2.9 |
| **Digestive system** | | |
| Dry mouth | 3.0 | 15.7 |
| Constipation | 6.0 | 12.9 |
| Gastroenteritis | 0.0 | 2.9 |
| Increased appetite | 0.0 | 2.9 |
| **Metabolic and nutritional disorders** | | |
| Edema | 0.0 | 12.9 |
| Peripheral edema | 6.0 | 10.0 |
| Weight gain | 0.0 | 4.3 |
| **Musculoskeletal system** | | |
| Myasthenia | 4.5 | 8.6 |

**Table 5.** Incidence (%) of Treatment-Emergent Adverse Events in a Placebo-Controlled Study in Neuropathic Pain Associated with Spinal Cord Injury (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

| **Body System Preferred Term** | **Placebo** | **Pregabalin 150 - 600 mg/day)** |
|---|---|---|
| | N = 67 | N = 70 |
| | % | % |
| **Body as a whole** | | |
| Joint disorder | 0.0 | 2.9 |
| **Nervous system** | | |
| Somnolence | 9.0 | 41.4 |
| Dizziness | 9.0 | 24.3 |
| Amnesia | 3.0 | 10.0 |
| Thinking abnormal[a] | 1.5 | 8.6 |
| Paresthesia | 1.5 | 5.7 |
| Euphoria | 0.0 | 4.3 |
| Speech disorder | 1.5 | 4.3 |
| Twitching | 0.0 | 4.3 |
| Withdrawal syndrome | 0.0 | 4.3 |
| **Skin and appendages** | | |
| Skin ulcer | 1.5 | 4.3 |
| Alopecia | 0.0 | 2.9 |
| Vesiculobullous rash | 0.0 | 2.9 |
| **Special senses** | | |
| Blurred vision[b] | 3.0 | 8.6 |
| Diplopia | 1.5 | 2.9 |
| Tinnitus | 0.0 | 2.9 |
| **Urogenital system** | | |

**Table 5.** Incidence (%) of Treatment-Emergent Adverse Events in a Placebo-Controlled Study in Neuropathic Pain Associated with Spinal Cord Injury (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

| **Body System Preferred Term** | **Placebo** | **Pregabalin 150 - 600 mg/day)** |
|---|---|---|
| | N = 67 | N = 70 |
| | % | % |
| **Body as a whole** | | |
| Urinary incontinence | 3.0 | 5.7 |

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Repchinsky C editor. Corticosteroids: Systemic monograph, Compendium of Pharmaceuticals and Specialties. Ottawa, Ontario: Canadian Pharmacists Association; 2007. p. 307-308.

| **Table 6. Dose modification and supportive measures*** | |
|---|---|
| **Pregabalin** | |
| ***Adverse event*** | ***Approach - Supportive measures*** |
| Angioedema (swelling face, mouth, neck throat, larynx/upper airway). | Should be immediately discontinued. Patient will be directed to the ER for appropriate supportive measures. |
| Hypersensitivity | Should be immediately discontinued. Patient will be directed to the ER for appropriate supportive measures. |
| Renal failure | Discontinuation should be considered. Patient will be directed to the ER for appropriate supportive measures. |
| Ophthalmological effects (e.g. amblyopia and diplopia) | Discontinue if visual disturbances persist. Ophthalmological assessments (if already routinely monitored, increase the frequency). |
| Peripheral edema | Patient will be directed to the ER for appropriate supportive measures. Renal function will be monitored. |
| Congestive heart failure | Patient will be directed to the ER for appropriate supportive measures. |
| Serious skin reactions (e.g. Stevens Johnson Syndrome) | Patient will be directed to the ER for appropriate supportive measures. |
| Gastrointestinal events (e.g. intestinal obstruction, constipation) | Caution when associating with opioid analgesics. Discontinue medication. Monitor vitals. Potentially manage with laxatives or enema. |
| Weight gain | Discontinue medication and monitor renal function. |
| Dizziness and Somnolence | Patients should be advised not to drive or operate complex machinery or engage in other hazardous activities until they have gained sufficient experience with pregabalin to gauge whether or not it affects their mental and/or motor performance adversely. |
| Suicidal behavior and ideation | Patient will be directed to the ER for appropriate supportive measures. |
| Encephalopathy | Patient will be directed to the ER for appropriate supportive measures. This adverse event was noted among patients with a history of kidney or liver disease. |
| Myopathy (diagnosed or suspected) with Creatine kinase elevation | Discontinue if patients report unexplained muscle pain, tenderness or weakness. Monitor function and hydrate. Patients who are taking over potentially myotoxic drugs (e.g. statins), should be aware of reports of adverse reactions. |

| **Table 6. Dose modification and supportive measures*** | |
|---|---|
| Significant CNS or respiratory depression | Patient will be directed to the ER for appropriate supportive measures. |
| Significant vomiting | Patient will be directed to the ER for appropriate supportive measures. |
| In patients with muscle pain, weakness or tenderness | Monitor creatine kinase for rhabdomyolysis. Monitor renal function. |
| Emergency room (ER).<br>Adverse events: Compendium of Pharmaceutics and Specialists, 2016<br>LYRICA (Pregabalin) Product Monograph. Kirkland, QC: Pfizer Canada Inc.; 2016: 1-62. | |

## 19.2. Appendix II: Celecoxib and Naproxen Adverse Events

The following adverse events mentioned on Table 6 occurred in 0.1 - 1.9% of patients regardless of causality.

**Table 7. Adverse events with the use of CELECOXIB (100 – 200 mg BID or 200 mg QD)**

| | |
|---|---|
| Gastrointestinal: | Constipation, diverticulitis, dry mouth, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, stomatitis, tenesmus, tooth disorder, vomiting |
| Cardiovascular: | Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction |
| General: | Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain |
| Resistance Mechanism Disorders: | Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media |
| Central, Peripheral Nervous System: | Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo |
| Female Reproductive: | Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage, vaginitis |
| Male Reproductive: | Prostatic disorder |
| Hearing and Vestibular: | Deafness, ear abnormality, earache, tinnitus |
| Heart Rate and Rhythm: | Palpitation, tachycardia |
| Liver and Biliary System: | ALT increased, AST increased, hepatic function abnormal |
| Metabolic and Nutritional: | Urea increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase |
| Musculoskeletal: | Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis |
| Platelets (bleeding or clotting): | Ecchymosis, epistaxis, thrombocythemia |
| Psychiatric: | Anorexia, anxiety, appetite increased, depression, nervousness, somnolence |
| Hemic: | Anemia |
| Respiratory: | Bronchitis**,** bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia |
| Skin and Appendages: | Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria |
| Application Site Disorders: | Cellulitis, dermatitis contact, injection site reaction, skin nodule |
| Special Senses: | Taste perversion |
| Urinary System: | Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection |
| Vision: | Blurred vision, cataract, conjunctivitis, eye pain, glaucoma |

**Table 8 lists all adverse events occurring in >2% of patients receiving Celecoxib from 12 controlled studies conducted in patients with osteoarthritis and rheumatoid arthritis that included a placebo and/or a positive control group.**

| | Celecoxib 100-200mg BID/200mg QD (n=4146) | **Placebo (n=1864)** | **Naproxen** 500mg BID **(n=1366)** |
|---|---|---|---|
| | **%** | **%** | **%** |
| Abdominal pain | **4.1** | **2.8** | **7.7** |
| Diarrhea | 5.6 | 3.8 | 5.3 |
| Dyspepsia | 8.8 | 6.2 | 12.2 |
| Flatulence | 2.2 | 1.0 | 3.6 |
| Nausea | 3.5 | 4.2 | 6.0 |
| Back pain | 2.8 | 3.6 | 2.2 |
| Peripheral edema | 2.1 | 1.1 | 2.1 |
| Injury-accidental | 2.9 | 2.3 | 3.0 |
| Dizziness | 2.0 | 1.7 | 2.6 |
| Headache | 15.8 | 20.2 | 14.5 |
| Insomnia | 2.3 | 2.3 | 2.9 |
| Pharyngitis | 2.3 | 1.1 | 1.7 |
| Rhinitis | 2.0 | 1.3 | 2.4 |
| Sinusitis | 5.0 | 4.3 | 4.0 |
| Upper respiratory tract infection | 8.1 | 6.7 | 9.9 |
| Skin Rash | 2.2 | 2.1 | 2.1 |

CELEBREX (celecoxib) Product Monograph. Kirkland, QC: Pfizer Canada Inc.; 2013: 1-53.

NAPROXEN EC (Naproxen Enteric-Coated Tablets), Brampton, Ontario: Sanis Health Inc. 2017:1-37.

Repchinsky C editor. Corticosteroids: Systemic monograph, Compendium of Pharmaceuticals and Specialties. Ottawa, Ontario: Canadian Pharmacists Association; 2007.

## 19.3. Appendix III: Interscalene Block

- **Interscalene block technique**
  - The interscalene block will be administered by a trained anaesthesiologist experienced in providing these blocks, approximately 1 hour prior to the start of the planned surgery in the block room.
  - The interscalene block consists of the administration of a single injection of local anaesthetic (bupivacaine 0.5% with epinephrine 5 μg/mL) under ultrasound guidance.
  - Patients will be positioned in supine or sloppy lateral decubitus position with surgical side slightly higher than the non-operative site.
  - After disinfection of the skin with chlorhexidine 0.5%, ultrasound gel will be applied to the area of the planned injection. The plexus will be localized using the "sweepback technique". This technique consists of gliding the ultrasound head between the middle and anterior scalene muscles.
  - Once the plexus is identified, 1-2cc of local anaesthetic will be used to freeze the skin. A short bevel block needle will be advanced towards the neural structures (C5, C6, or the upper trunk) of the brachial plexus.
  - Between 5 and 15 mL of the local anaesthetic (or bupivacaine 0.5% with epinephrine 5 μg/mL) will be injected. The recommended dose for brachial plexus block (which includes an interscalene block) for adults is bupivacaine 0.5% with epinephrine 5 μg/mL not to exceed 30 mL.
  - A sterile dressing will be applied to the puncture site.
  - After confirmation of a local anesthetic effect, the patient will then be transferred to the surgical suite.

- **Interscalene Block (Block) Adverse events**

Misamore *et al*. reported transient adverse events in 142 of 910 patients (16%) receiving an interscalene block (Block). These included Horner's Syndrome (8.8%), recurrent laryngeal nerve dysfunction (2.0%), mild dyspnea (1.5%), and severe dyspnea (0.6%). These adverse events often resolved within 24 hours. Persistent neurological complications (greater than 6 months) can occur in less than 1%. The most common adverse events are paresthesia, dysesthesia and hypesthesia.

- **References**

Misamore G, Webb B, McMurray S, Sallay P. A prospective analysis of interscalene brachial plexus blocks performed under general anesthesia. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons [et al]* 2011; **20**(2): 308-14.

## 19.4. Appendix IV: Bupivacaine Adverse Events

- Adverse reactions to local anesthetics are very rare in the absence of overdose or inadvertent intravascular injection. With the introduction of US-guided injections, the risk of intravascular injections has been significantly reduced. Most of the adverse events were from the effects of the block and the clinical situation, rather than the reaction to the drug.
- Allergic type reactions are rare and may occur as a result of sensitivity to local anesthetics of the amide-type.
- Acute systemic toxicity from local anesthetics is generally dose-related and due to high plasma levels, which may result from over dosage, rapid absorption from the injection site, diminished tolerance, or from inadvertent intravascular injection.
    - For this pilot study, the technique described for an interscalene block uses a dose of 5-15 mL of 0.5% (25 to 75mg) of bupivacaine injected under direct imaging. This dose injected into the venous system is not expected to result in acute systemic toxicity in an adult.
- Based on all clinical studies, the two symptoms hypotension and nausea are the most common. Dizziness, vomiting, back pain, fever, rigor, slow or fast heartbeat, headaches, pins and needles sensation, difficulty passing urine are also described. With the exception of pin and needles sensation these side effects are not expected with peripheral nerve block.
- Most commonly, the acute adverse experiences originate from the central nervous and cardiovascular systems. These are listed below:
    - Central Nervous System: Restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, nausea, vomiting, chills, paresthesia, hyperacousis, and dysarthria. Nerve trauma, neuropathy, urinary retention, diplopia and spinal cord dysfunction have been associated with regional anesthesia.
    - Cardiovascular System: High doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, hypertension, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and cardiac arrest.
    - Elevation of Body Temperature**:** Epidural infusion of NAROPIN has, in some cases, been associated with transient elevations in body temperature to >38.5°C.

**References**

MARCAINE (bupivacaine), Product Monograph, Kirkland, QC: Pfizer Canada Inc.; 2018:1-40
NAROPIN (ropivacaine), Product Monograph, Aspen Pharmacare Canada Inc; June 12, 2018:1-42.

## 19.5. Appendix V: Adverse Events with medications used at normal practice

| Dexamethasone |
| --- |
| Most of the adverse event associated with dexamethasone occur with prolonged use. With single dose administration the adverse events include short term elevation in blood glucose for those with diabetes mellitus. |
| Fluid and electrolyte disturbances: sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension. |
| Musculoskeletal: muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones, tendon rupture. |
| Gastrointestinal: nausea, vomiting, anorexia which may result in weight loss; increased appetite which may result in weight gain; diarrhea or constipation, abdominal distention, pancreatitis, gastric irritation and ulcerative esophagitis; peptic ulcer with possible perforation and hemorrhage; perforation of the small and large bowel particularly in inflammatory bowel diseases. |
| Dermatologic: Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; striae; hirsutism; acneiform eruptions; suppressed reactions to skin tests; hypersensitivity reactions such as allergic dermatitis, urticaria, angioneurotic edema. |
| Neurologic: Seizures; increased intracranial pressure with papilledema (pseudotumor cerebri) in association with withdrawal of corticosteroid therapy; convulsions; vertigo; headache; psychic disturbances; neuritis; paresthesias. |
| Endocrine: Decreased carbohydrate tolerance; hyperglycemia; glycosuria; increased requirements for oral hypoglycemics or insulin in diabetes; manifestations of latent diabetes mellitus; menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; hirsutism; increased sweating. |
| Ophthalmic: Increased intraocular pressure; glaucoma; exophthalmos; posterior subcapsular cataracts. |
| Metabolic: Negative nitrogen balance due to protein catabolism. |
| Psychologic: Hallucinations; psychosis; euphoria; mood changes. |
| Cardiovascular: Thromboembolism; fat embolism; hypercholesterolemia; accelerated atherosclerosis; cardiac arrhythmias or ECG changes due to potassium deficiency; syncope; aggravation of hypertension. |
| Hematologic: Leukocytosis, thrombocytopenia, lymphopenia. |
| Allergic Reactions: Anaphylactoid reaction, anaphylaxis, angioedema. |

| Acetaminophen |
| --- |
| Agranulocytosis: unexplained sore throat and fever |
| Anemia: unusual tiredness or weakness |
| Dermatitis, allergic: skin rash, hives, or itching |
| Hepatitis: yellow eyes or skin |
| Renal colic: pain, severe and/or sharp, in lower back and/or side with prolonged use of high doses in patients with severe renal function impairment. |
| Renal failure: sudden decrease in amount of urine, uremia may result, especially with prolonged use of high doses in patients with severe renal function impairment; also, although a causal association has not been established a retrospective study has suggested that long term daily use of acetaminophen may be associated with an increased risk of chronic renal disease (analgesic nephropathy) in individuals without pre-existing renal function impairment. |
| Thrombocytopenia usually asymptomatic: rarely, unusual bleeding or bruising; black, tarry stools; blood in urine or stools; pinpoint red spots on skin |
| **Tramadol** |
| Addiction, Abuse, and Misuse. TRAMADOL poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. |
| Serious, life-threatening, or fatal respiratory depression may occur with use of TRAMADOL. Patients should be monitored for respiratory depression, especially during initiation of TRAMADOL or following a dose increase. |
| Seizure Risk |
| Cardiovascular Tramadol administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. |
| Gastrointestinal Effects: Tramadol and other morphine-like opioids have been shown to decrease bowel motility. Tramadol may obscure the diagnosis or clinical course of patients with acute abdominal conditions |
| Neurologic: Serotonin Syndrome: TRAMADOL could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g., anti-depressants, migraine medications). |
| Psychomotor Impairment: TRAMADOL may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of tramadol with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol. |
| Respiratory Depression: Administer TRAMADOL cautiously in patients at risk for respiratory depression. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol hydrochloride are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures |

Sexual Function/Reproduction: Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility

**Ondansetron**

Cardiovascular: There have been rare reports of tachycardia, angina (chest pain), bradycardia, hypotension, syncope and electrocardiographic alterations.

Central Nervous System: There have been rare reports of seizures. Movement disorders and dyskinesia have been reported in two large clinical trials of ondansetron at a rate of 0.1 - 0.3%.

Dermatological: Rash has occurred in approximately 1% of patients receiving ondansetron.

Hypersensitivity: Rare cases of immediate hypersensitivity reactions sometimes severe, including anaphylaxis, bronchospasm, urticaria and angioedema have been reported.

Metabolic: There were transient increases of SGOT and SGPT of over twice the upper limit of normal in approximately 5% of patients. These increases did not appear to be related to dose or duration of therapy. There have been reports of liver failure and death in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear. There have been rare reports of hypokalemia.

Other: There have been reports of abdominal pain, weakness and xerostomia.

Special Senses: Rare cases of transient visual disturbances (e.g. blurred vision) have been reported during or shortly after intravenous administration of ondansetron, particularly at rates equal to or greater than 30 mg in 15 minutes.

- **References**

Repchinsky C editor. Corticosteroids: Systemic monograph, Compendium of Pharmaceuticals and Specialties. Ottawa, Ontario: Canadian Pharmacists Association; 2007. p. 307-308.

Dexamethasone (sodium phosphate injection USP) Product Monograph. Omega Laboratories Limited. June 12, 2012.

Acetaminophen Product Monograph. Montreal, QC: Pendopharm; 2017: 1-18.

Tramadol (Tramadol Hydrochloride Tablets) Product Monograph: Vaughan, Ontario: AA Pharma Inc. 2018:1-50.

Ratio-ONDANSETRON (ondansetron hydrochloride dihydratetablets, Product Monograph: Toronto, Ontario: ratiopharm inc.; 2012:1-26.

## 19.6. Appendix VI: Pilot observation data

We have pilot observational data at 1-day post-surgery in patients who would meet our inclusion criteria, from one of the recruiting sites (St Mary's Hospital Centre. Fourteen patients who underwent arthroscopic shoulder surgery received PMC. Block alone was not assessed because it is not part of the standard care, and no ethics approval was sought. Of these patients, 11 received a block with their PMC because of anesthesiologist preference, and 3 received PMC alone. At 1-day post-surgery (the time point for our primary outcome), the mean (SD) pain was 4.1 (1.8) for PMC+Block and 1.6 (1.6) for PMC alone. Although based on very small numbers, these results support the efficacy of the PMC regimen (minimal important difference = 2) (81,82) for pain at 24 h, as suggested by the rebound pain with block resolution hypothesis (26). At 6 hrs, the mean of the PMC+Block and PMC groups were 1.2 (2.1) and 3.7 (1.8), respectively.

The results are consistent with the expected efficacy of PMC+Block while the short-lived Block anesthetic effect is still present. At 1 week, the mean of the PMC+Block and PMC groups were 4.0 (2.0) and 4.2 (2.1), respectively. Even if the reduction in pain does not last 1 week, the benefits of PMC at 1 day might represent considerable reduction in suffering, and possibly reduce routine opioid use. We have also found that 2 out of 8 PMC patients were less likely to use opioids for rescue medication compared to 7 of 8 patients receiving standard opioid-based pain management.

## 19.7. Appendix VII: Study Schedule

| | Screening/ Enrollment Rando/Baseline | **Pre-operative days (D1-5)** | | | | | **Surgery (D6)** | | **Post-operative days** Follow-up | | | | **End of Study FU/ Final visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Block | Surgery | 6h | 1d | 1w | 2m | 6m |
| Clinic Visits | V0.0 | | | | | | V1.0 | | | | | V2.0 | V3.0 |
| Days | **D-21 to D0** | **D1** | **D2** | **D3** | **D4** | **D5** | **D6[(1)]** | **D6** | **D6** | **D7** | **D13** | **D66** | **D186** |
| **Informed consent signed** | X | | | | | | | | | | | | |
| **Inclusion/exclusion** | X | | | | | | | | | | | | |
| **Demography** | X | | | | | | | | | | | | |
| **Medical history/ prior medications** | X | | | | | | | | | | | | |
| **Blood Tests**[2] | X | | | | | | | | | | | | |
| **POQ** | X | | | | | | | | | | | | |
| **PHQ-4** | X | | | | | | | | | | | | |
| **Study drug** | | | | | | | | | | | | | |
| - PMC+Block | | X | X | X | X | X | X | X | | | | | |
| - Block | | - | - | - | - | - | X | X | | | | | |
| **Participant diary** | | | | | | | | | | | | | |
| - Medications | | X | X | X | X | X | | | | | | | |
| - Concomitant medications | | X | X | X | X | X | | X | X | X | X | X | X |
| **- AE recording** | | X | X | X | X | X | X | X | X | X | X | X | X |
| **Phone call FU** | | | | | | | | | | | | | |
| - Pre-surgery Rx | X | | | X | | X | | | | | | | |
| - POQ (pain intensity) | | | | X | | X | | | X | X | X | X | X |
| - POQ (physical activity) | | | | | | | | | | | | X | X |
| - Concomitant medications | | | | X | | X | | | | X | X | X | X |
| - **AE** | | | | X | | X | | X | X | X | X | X | X |

Abbreviations: AE=adverse events; POQ=Patient Outcome Questionnaire; PHQ-4=Patient Health Questionnaire-4; Day 0 is considered as day of randomization
[1]Block: performed 1 h before surgery; [2]Lab tests (creatinine), if not done in previous 12 months.
Concomitant medications will be assessed at 6 hours, 1-day, 1 week, and 2 and 6 months after surgery
All AEs will be recorded on the AE Forms of the eCRF from information obtained at each assessment time or when otherwise volunteered by the subject.

## 19.8. Appendix VIII: Essential Documents - Pre Trial

**Table 1. Before the Clinical Phase of the Trial Commence**

| Title Of Document | Located In Files Of | |
|---|---|---|
| | Investigator/ Institution | Sponsor |
| **Investigator's Brochure** | X | X |
| **Signed Protocol and Amendments, If Any, And Sample Case Report Form (CRF)** | X | X |
| **Information Given To Trial Subject**<br>- Informed Consent Form<br>- Any other written information<br>- Advertisement for Subject Recruitment, if used | <br>X<br>X<br>X | <br>X<br>X |
| **Financial Aspects of The Trial** | X | X |
| **Insurance Statement** (where required) | X | X |
| **Signed Agreement Between Involved Parties,** e.g.:<br>- Investigator/Institution And Sponsor | X | X |
| **Dated, Documented Approval/Favourable Opinion Of Institutional Review Board (IRB) /Independent Ethics Committee (IEC)** | X | X |
| **Institutional Review Board/Independent Ethics Committee Composition** | X | X<br>(where required) |
| **Regulatory Authority(ies) Authorisation/Approval/ Notification Of Protocol** (where required) | X<br>(where required) | X<br>(where required) |
| **Curriculum Vitae And/Or Other Relevant Documents Evidencing Qualifications Of Investigator(s) And Sub-Investigator(s)** | X | X |
| **Normal Value(s)/Range(s) For Medical/Laboratory/Technical Procedure(s) And/Or Tests Included in the Protocol** | X | X |
| **Master Randomisation List** | | X |
| **Pre-Trial Monitoring Report** | | X |
| **Trial Initiation Monitoring Report** | X | X |

## 19.9. Appendix IX: Essential Documents: Maintained by the Investigator at the Study Site – During Trial

**Table 1. During the Clinical Conduct of the Trial**

| √ or N/A | Document Type/Name |
|---|---|
| | Investigator Brochure, Addenda (Including Safety updates) and revisions |
| | Approved Protocol and amendments signed and dated by the Investigator |
| | Administrative Letters processed |
| | Decoding procedures for blinded trials, if not included in the protocol |
| | Blanket Corrections Document (signed by Investigator) |
| | Signed FDA 1572 or signed QI Undertaking form |
| | Current CV of Qualified Investigator or sub-investigator indicating affiliation at study site (full or abbreviated CV) |
| | Document of submission by Investigator to IRB/IEC of:<br>- IB, Safety Updates, Addenda & Revisions<br>- Protocol, Amendments, Administrative letters<br>- CRF, if required locally<br>- Informed Consent Form (ICF)<br>- Written information provided to subjects<br>- Advertisement for subject recruitment<br>- Subject compensation<br>- Any other documents requested by the IRB/IEC |
| | Name and address of IRB/IEC including name of Chairperson |
| | Dated, documented approval/favorable opinion of IRB/IEC of the following, as applicable:<br>- Protocol, Amendments<br>- Administrative Letters (if required locally)<br>- Informed Consent Form<br>- Written information to be provided to subjects<br>- Advertisement for subject recruitment<br>- Subject compensation<br>- Any other documents requested by the IRB/IEC |
| | IRB/IEC composition to document that IRB/IEC is constituted in compliance with ICH GCP and local regulatory requirements:<br>- listing of members by occupation and affiliation or<br>- letter from chairperson stating that the IRB/IEC is in accord with applicable regulations and guidelines |
| | Copy of IRB/IEC approved informed consent form and any other information provided to subjects |

If the Investigator, or other study personnel, is a member of the IRB/IEC, documentation from the IRB/IEC indicating that he/she did not vote on approval of the protocol or amendments

Correspondence between the Investigator and the IRB/IEC

Documentation that the Investigator forwarded SAE reports, related reports of safety information to IRB/IEC

Normal values/ranges for medical/technical/laboratory procedures/tests required by protocol

Trial initiation monitoring report/letter to site to document trial procedures were reviewed with Investigator

Trial initiation training materials e.g. Investigator Meeting, annotated CRF, correspondence

Evidence of monitoring by the sponsor (CRO), e.g., Monitoring Log, Follow-up Letters

Clinical Supplies Documentation :

Informed consent form signed and dated by subjects prior to participation to the trial

Original source documents substantiating trial data collected

Delegation of Authority Form- documenting signature/initials of persons authorized to enter/correct CRF data

Copies of signed, dated CRFs including copies of CRF corrections and SAE reports

Subject Screening Log

Subject Enrolment Log

Signed agreement between involved parties:

- investigator/CRO

Insurance/indemnity statement where applicable

Completed Financial Disclosure forms, if applicable

Interim or annual report to IRB/IEC and Health Authorities

IRB/IEC notice of study closure

Other items if required by applicable regulations and guidelines:
- Health Authority approval/notification
- Interim or annual reports to IRB/IEC and Health Authorities
- Final report to IRB/IEC and Health Authorities
- IRB/IEC notice of study closure