**Study Protocol**

**Title: “VOLT ACL Study : Intraosseous Regional Administration of Diclofenac in Anterior Cruciate Ligament Reconstruction”**

**Version 1**

**Date: 01/09/24**

**A prospective, double-blinded, randomised controlled trial of Intraosseous Regional Diclofenac vs. Intravenous Diclofenac for Postoperative Pain Management in Anterior Cruciate Ligament Reconstruction**

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**Background:**

Anterior cruciate ligament (ACL) rupture is a common injury many athletes suffer, typically from a non-contact pivoting mechanism [1,2]. It is a critical stabilising structure in the knee that acts as the primary restraint for anterior tibial translation and provides rotational stability. The New Zealand ACL Registry showed that as of August 2023, 19,881 patients had been enrolled in the registry, with 17,950 primary ACL reconstructions (ACLRs) and 1,931 revisions performed [3]. The incidence of ACLRs has been steadily increasing each year [4].

Surgery for ACL reconstruction is associated with moderate to severe pain in the immediate postoperative period. Thus, with the likelihood that more ACLRs will be performed in New Zealand, effective analgesia is needed to ensure early mobilisation, timely discharge, functional recovery, patient satisfaction, and minimise re-admissions [5,6].

Multimodal analgesia in ACLR

Various modes of analgesia have been trialled following ACLR, including oral, regional, local intra-articular, and spinal analgesia [5-10]. A meta-analysis by Maheshwer sought to compare spinal analgesia, regional analgesia (femoral nerve block (FNB), adductor canal block (ACB)), and local analgesia [11]. The study showed that whilst the results were heterogeneous, the Visual Analogue Scale (VAS) scores for pain were lower in regional blocks than spinal blocks between 8 and 12 hours post-operation. The pooled mean VAS score for regional blocks was 2.87 and 4.32 for spinal blocks (p < 0.01). However, there was no significant difference in VAS scores amongst the three analgesia groups at 12-24 hours. Within regional blocks, FNB were more effective than ACB at 12-24 hours. Another meta-analysis by Hussain showed that all forms of regional blocks (FNB, ACB, sciatic nerve block) were superior to oral analgesia [12]. Although evidence suggests that FNBs are effective in reducing postoperative pain, the disadvantage of using FNBs is that they are known to create delayed rehabilitation and risk of falls due to the loss of motor function of the quadriceps muscles [11].

Oral analgesia following ACLRs often includes the usage of opioids, which are effective in reducing pain but include adverse effects such as sedation, respiratory depression, confusion, nausea, vomiting, constipation, and urinary retention [13]. Consequently, such complications have led many providers to modify their analgesia regime to involve fewer opioids and look towards other options [14].

NSAIDs in Multimodal Analgesia

Non-steroidal anti-inflammatory drugs (NSAIDs) form part of the multimodal approach for analgesia, providing analgesic effects whilst also having anti-inflammatory and antipyretic properties, which aid in recovery by dampening the inflammatory phase of healing. [15]

The usage of NSAIDs in ACLRs for pain relief has been investigated thoroughly and has proven efficacy in reducing postoperative pain and opioid consumption [5,6,16]. In a triple-blinded, randomised controlled trial, celecoxib as a pre-emptive analgesic after ACLR was effective in reducing pain intensity and opioid consumption at 6 and 24 hours post-operatively [17].

Intravenous and Intraosseous Regional Administration

Intravenous regional administration (IVRA), also known as "Bier's block", is another method of administering local anaesthetics. IVRA involves administering local anaesthetic into a vein, with an inflated tourniquet placed proximal to it [18]. This method prevents venous blood flow beyond the tourniquet, ensuring that the local anaesthetic is only distributed throughout the area of interest distal to the tourniquet, and higher local tissue concentrations are achieved. Studies have shown that NSAIDs are effective in improving postoperative pain when used with IVRA [18-22]

In the lower limb, IVRA requires cannulation of a foot vein, which can be difficult. The intraosseous route is an alternative, as intraosseous access can be easier to obtain and distribution of injected medication is equivalent to intravenous, it may be preferred for lower limb procedures such as ACL reconstruction. For procedures conducted on the lower limb in particular, IORA of local anaesthetics would typically be performed on the anteromedial aspect of the proximal tibia, 2 cm inferior to the medial joint line, at the level of the tibial tuberosity [23]. This area has a thinner cortex with a thin layer of skin and soft tissue, making it an accessible site for introducing an intraosseous cannula.

Medication administration into the metaphyseal bone has also been found to result in faster flow rates. The intraosseous route allows the medication to pass through the medullary cavity into the systemic venous circulation without concern for venous collapse, such as in intra-venous access [23]. Studies have shown that IORA for prophylactic antibiotics during total knee arthroplasty (TKA) yields a 10-20 times higher local concentration than systemic intravenous administration [24].

Other potential advantages of using IORA include minimising systemic adverse effects of oral analgesia such as renal toxicity, with potential indirect benefits of reducing opioid consumption and optimising rehabilitation with better postoperative analgesia.

Three studies have shown promise for the use of IORA analgesia following total knee arthroplasty.[25,26]. Brozovich demonstrated efficacy in the use of IORA morphine in TKA [25], whilst McNarama reported for IORA multimodal analgesia in TKA after showing significantly better pain control in patients receiving ketorolac+morphine versus morphine only. [26]

The third trial, performed by our research group, enrolled forty-six primary TKA patients (twenty-three per group) in a prospective, double-blinded, randomised controlled trial. The intervention group received 75 mg IORA Diclofenac and IV normal saline placebo. The control group received 75 mg IV Diclofenac and IO normal saline placebo. We found IORA Diclofenac provided enhanced early postoperative pain relief, reduced opioid consumption, with better early knee function and patient satisfaction. The study was recently awarded the Clinical Research Award at the American Association of Hip and Knee Arthroplasty Surgery meeting in Dallas in November 2024.

Safety of IORA in ACL Surgery

The potential complications related to IORA include fluid extravasation around the puncture site, bone fracture, infection, and possible compartment syndrome when the needle passes two cortices [23]. However, these complications are exceedingly rare (<1%) and have been reported in the emergency setting rather than in the more controlled environment of the operating room.

A theoretical concern with NSAIDs is a potential negative effect on bone healing [27]. The bone-patellar tendon-bone (BPTB) graft ACLR technique is frequently used, and this technique requires bone-to-bone healing [28]. The literature on this topic mainly involves studies assessing the effect of NSAIDs on fracture healing. Findings from animal studies are mixed, with some studies using rat or rabbit models of fracture suggesting NSAIDS have a negative influence on bone healing, and others studies reporting no difference. [29-31,32]. A recent meta-analysis of RCTs investigating the effect of NSAIDs on fracture healing in humans found no effect of short term NSAIDs on fracture union, and clinical practice guidelines recommend their continued use following fracture [33,34].

Two human studies have investigated the impact of NSAIDs following ACLR on outcome. In a registry study by Soreide et al., patients administered NSAIDs postoperatively following ACLR showed no difference in graft survival, risk of revision, or patient reported outcome measures at two years follow-up. [35] Furthermore, performed a trial on hamstring tendon ACLR and celecoxib compared to tramadol , and found no difference in stability or clinical outcomes. [36] Overall, NSAIDs appear safe following ACLR and are widely used. In addition, the senior author has used IORA diclofenac in over 400 primary ACL reconstructions, with no negative impact on revision rates or patient reported outcomes recorded by the New Zealand ACL registry, which tracks all ACL reconstructions in New Zealand.

IORA in ACLR

To the best of our knowledge, only one study has investigated the effect of IORA analgesia on ACLR. In a pilot study, Stowers et al. investigated the safety of intraosseous versus local infiltration ropivacaine, a local anaesthetic (ie a Beir’s block). There was no difference in safety outcomes seen in the study between IORA and local infiltration. [37]

The combination of the advantages of IORA forms the basis for our study in investigating the potential for IORA of Diclofenac in ACLR.

Rationale for study:

We hypothesise that IORA of analgesia may be advantageous over other forms of administration, namely:

1. The ability to deliver analgesic medication directly to the surgical area of interest and avoid systemic delivery, thus minimising systemic adverse effects.
2. Achieving a “pooling effect” with tourniquet use, therefore maximising duration and concentration analgesia at the surgical site, resulting in overall more efficacious pain relief.
3. Possible lower postoperative systemic opiate consumption due to more effective pain relief, therefore alleviating the burden of opiate side effects.
4. More rapid regional administration of medications by circumventing the need to cannulate foot veins allows for increased turnover and efficiency of the operating theatre and hospital system.

Patient evaluation schedule:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Measure | Pre-operatively | Post-operative hours 1, 2, 3 (and all subsequent hours if not yet discharged) | Post-operative day 1 | Post-operative day 2,3,4,5,6,7 | 2 week post-operatively | 8 weeks post-operatively |
| Demographics | x |  |  |  |  |  |
| Medical History | x |  |  |  |  |  |
| Pre-operative analgesia | x |  |  |  |  |  |
| Tampa Scale of Kinesiophobia 11 (TSK-11) | x |  |  |  |  |  |
| Lysholm | x |  |  |  | x | x |
| Knee injury and Osteoarthritis Outcome Score - Quality of Life (KOOS-QoL) | x |  |  |  | x | x |
| Visual Analogue Scale (VAS) Pain at Rest | x | x | x | x |  |  |
| Visual Analogue Scale (VAS) Pain at Mobilisation | x | x | x | x |  |  |
| Morphine in Milligrams Equivalent (MME) | x | x | x | x |  |  |
| (Quality of Recovery-15) QoR-15 |  |  | x |  |  |  |
| Numeric Rating Scale (NRS) for Sleep |  |  | x | x |  |  |

**Visit Windows**

Definition – Since it is not always possible for subjects to come in for a study visit on the exact date, most protocols allow a certain time period before or after the calendar date; this is known as the visit window. If a subject is not seen during the visit window, that visit will be regarded as a missed visit. Visit windows are calculated in reference to the baseline date, which is the surgery date (intra-op) for this study.

Visit windows:

* Pre-op: within 6 months before date of surgery
* Week 2: +/- 1 week
* Week 8: +/- 2 weeks

**Objectives:**

Primary objective:

* To demonstrate that preoperative IORA Diclofenac (VoltarenTM) is superior to systemic (IV Systemic) Diclofenac, in providing postoperative analgesia after primary ACLR. VAS pain at rest and movement will be the primary outcome measured during early recovery (immediately post-op and at 1-week follow-up).

Secondary objectives:

* Dosage and frequency of opioid consumption post-operation, and comparisons of MME between IORA and systemic diclofenac
* Quality of life and functional outcomes – Lysholm and KOOS-QoL, numerical rating scales (NRS) of sleep
* Post-operative recovery comparisons using the Quality of Recovery 15 (QoR-15) survey

Questions to be answered:

1. Does IORA diclofenac provide greater pain control in the immediate and short postoperative period and therefore a reduction in opioid consumption?
2. Will IORA diclofenac result in greater quality of life and functional outcomes as compared to systemic diclofenac?
3. Is there any difference in early postoperative (<8 weeks) complications (eg infections, readmissions, wound healing, thromboembolism) between IORA and systemic intravenous (IV) administration of diclofenac in ACLR?

**Study Design**

A prospective, double blinded RCT, with a two-site cohort.

**Patients and Methods**

* All patients who will be undergoing primary BPTB ACLR for ACL rupture will be eligible for this prospective study.
* Patients will be randomised into two groups:
	+ IORA Diclofenac 75mg (intervention)
	+ IV Diclofenac 75mg (control)

**Inclusion Criteria**

* All patients over the age of 18 giving written consent
* Primary ACLR for ACL rupture

**Exclusion criteria**

- No capacity to consent to research project

- Allergy to NSAIDs

- History of severe asthma

- History of haemorrhagic diathesis

- History of gastrointestinal issues (peptic ulcers, gastrointestinal bleeding, and other significant gastrointestinal disorders at higher risk of complications following NSAID use)

- Significant renal impairment (GFR<30 mL/min/1.73m2)

- Severe hepatic disease

- Significant cardiac history

- Pregnancy or breastfeeding

- Clinically poorly controlled mental health

- Prior ipsilateral ACL surgery

- Patients with lower limbs not amenable to effective tourniquet use

- Precluded from having general anaesthesia

- Preoperative hypertension (systolic BP >180 mmHg)

- Significant use of analgesia at baseline (eg opioid dependence)

**Evaluations/Patient Outcome Measurements**

Patient demographics:

A record of the patient’s date of birth, age, gender, weight, height, BMI, and medical history will be obtained pre-operatively at time of consent.

Pre-operative analgesia:

A record of the patient’s average daily analgesic use in the week prior to surgery.

Lysholm:

Consists of 8 items that evaluate symptoms, daily activities and sports function in patients with knee injuries or conditions. Total scores range from 0 - 100 with higher scores indicating better function.

KOOS-QoL:

A subset of the KOOS questionnaire to assess a patient’s quality of life. This subsection includes 4 items with score ranging from 0 - 100 with higher scores reflecting better quality of life.

VAS Pain at rest and at mobilisation:

A graphic VAS will be used as a measurement instrument for patients to indicate their level of pain on a scale from ‘No Pain’ to ‘Worst Pain Possible’. VAS is a continuous spectrum to represent pain.

MME:

MME is the amount of morphine in milligrams equivalent to the strength of the opioid dose prescribed. This measurement will allow for a standardised comparison of opioid use between study groups.

Quality of Recovery (QoR-15):

A patient-reported outcome questionnaire to measure the quality of recovery after anaesthesia, which is important in determining early postoperative health status of patients.

Sleep:

NRS (0-10) for grading how pain has interfered with a patient’s sleep over the past 24 hours, from ‘does not interfere’ to ‘completely interferes’.

**Study procedure**

**Consenting:**

A study investigator will verbally inform potential study candidates of the purpose of the study, study duration, relevant procedural details, and study evaluations. Benefits that may result from the trial (during the study and for future patients) will be discussed, and also any foreseeable risks. Patients will then be given time to read, understand, and ask questions about the patient information sheet, and sign the study-specific Participant Consent Form if agreeable to participating in the study. Confidentiality of the participants will be maintained at all times, and de-identified patient information will be used during study analysis.

Participants will be informed that they are free to refuse participation, and medical care will not be compromised if they decline or withdraw from the study.

In order to be enrolled in the study, a signed and dated Participant Consent Form must be obtained first. The original will be kept by the investigator, with a copy being provided to the patient, and another copy placed in the patient’s hospital medical record.

Should a patient undergo any study procedure without signing a Participant Information and Consent Form, the Investigator must notify the applicable Ethics Committee of the deviation, detailing the circumstances which resulted in the failure to obtain informed consent. The Investigator will then follow Ethics Committee instructions on how to handle the patient/situation and obtain consent.

**Randomisation:**

*Allocation Concealment*

This will be achieved via a randomisation process using computerised sequence generation (random number generator) in a 1:1 ratio. Sealed, opaque envelopes which have been sequentially numbered will be used as the method of concealment. The envelopes will contain a randomised group allocation and instructions of medication preparation for administration. These will be prepared by an independent member of staff. The envelopes are to be sequentially numbered, as per the generated sequence, in advance for allocation to patients once they have consented to the trial. Once a patient has met the criteria for enrolment and has given informed consent, they will be allocated a randomisation envelope by the investigator or designee. Envelopes will be opened sequentially only after the participant’s name has been written on the appropriate envelope. The investigator or designee will note the randomisation number in the patient’s Case Report Form and this will be used as the patient’s study ID number. Patients will be blinded to their group allocation.

A patient information leaflet will be provided to the patient at their preoperative clinic appointment. Randomisation is to occur at the time of consent (which is usually the day prior to surgery) to allow for the appropriate orders to be made to ensure the study medication can be administered on time. The assigned envelope will be handed to a researcher on the day of the procedure, who will begin preparing the study medication for the appropriate study group.

 *Blinding*

Patients, surgeons, and anaesthetists will be blinded to group allocation. An unblinded researcher will prepare a 10 ml syringe with either normal saline 0.9% (control group), or 75mg Diclofenac made up to 10 mL with normal saline 0.9% (intervention group). The fluid will be passed onto the sterile field for administration by the treating surgeon.

An infusion of either 75mg Diclofenac made up to 100 mL with normal saline 0.9% (control group), or 100 mL normal saline 0.9% (intervention group) will be prepared by an unblinded researcher and handed over to the anaesthetist (blinded) for the preoperative IV infusion.

**Pre-operation:**

The following outcome measurements will need to be completed by patients prior to their surgery.

Baseline scores will be averaged for each study group:

* Preoperative VAS-pain score
* Preoperative TSK-11 score
* Preoperative Lysholm score
* Preoperative KOOS-QoL score
* Preoperative opioid use (MME) - Participants will be required to report any and all opioid pain medications (including Tramadol and Codeine) they use as well as the average daily amount of opioid medications in milligrams that they take. For example, 20 mg of Sevredol daily. This will be converted into a preoperative baseline MME.

**During operation:**

A single surgeon who regularly performs ACLR using BPTB will be included in this trial. Prior to all operations, each patient will undergo a general anaesthetic (GA) for their procedure, with no adjunctive peripheral nerve blocks. This will involve total IV anaesthesia with IV Propofol and IV fentanyl, as well as Ketamine and/or Clonidine in small amounts as adjuncts to the GA. The airway will be maintained via laryngeal mask airway.

The patient will then be positioned appropriately for surgery and a single cuff tourniquet applied to the upper thigh of the marked limb. Following standard patient preparation and draping of the appropriate limb, the limb is exsanguinated, and the tourniquet inflated to cease blood flow in the limb at 250-300 mmHg for the duration of the procedure (60-90 minutes). A proximal tibial intraosseous (IO) cannula will then be inserted, and the study medication administered into bone immediately before skin incision.

For the patients randomised to the intervention group, 75mg Diclofenac (75 mg/3 mL ampoules) will be made up to 10mL with normal saline 0.9% in a syringe to dilute the medication prior to administration. The medication will then be injected as a bolus by the blinded surgeon. Immediately after, 500 mg of Vancomycin in 110 mL normal saline 0.9% will be delivered intraosseously. These patients will also receive a preoperative IV infusion of 100 mL normal saline 0.9% over 2 minutes by the blinded anaesthetist. The infusion will finish at least 3 minutes prior to tourniquet inflation.

The patients randomised into the control group will receive 10mL of normal saline 0.9% will be given via IO after tourniquet inflation, followed by the same preparation of Vancomycin by the blinded surgeon. An IV infusion over 2 minutes of 75mg Diclofenac (75mg/3 mL ampoule) diluted to 100 mL with normal saline 0.9%, to finish at least 3 minutes prior to tourniquet inflation, will be administered by the blinded anaesthetist. Diclofenac (VoltarenTM) 75mg/3mL solution has been approved by New Zealand Medsafe for intravenous infusion, but requires to be diluted. There are injectable Diclofenac formulations which can be administered as bolus, however these are not available in New Zealand.

An unblinded researcher (not the surgeon or anaesthetist) will prepare the medication as described above, according to the participant’s group allocation. The preparation for IV infusion will be given to the blinded anaesthetist, and the preparation for IO injection will be given to the blinded surgeon.

All patients will also receive intraoperative local infiltration anaesthesia prior to skin closure in the form of 150 mL of 0.2% Ropivacaine with 0.3mcg of Adrenaline 1:1000 (0.3 mL). Weight based dosage of ropivacaine will be used if patients are under 70kg.

Patients in all study groups will receive a standardised regimen of pain relief (unless certain medications are contraindicated) postoperatively as an inpatient and on discharge. Postoperative analgesia includes IV Morphine boluses of 1-2 mg (in recovery only), Paracetamol 1 g PO QID, Celecoxib (dose will be prescribed according to weight/age), Tramadol modified release 100 mg PO BD, Gabapentin (dose will be prescribed according to weight/age), and Sevredol 10 mg PO Q1H PRN. The same preparation of Paracetamol, Celecoxib, Tramadol, and Gabapentin will be prescribed on discharge, but Sevredol will be reduced to 10 mg PO Q4H.

**Post-operation:**

**Primary Outcome: VAS-pain at rest and movement**

During the first hours post-operation, patients will be provided VAS by a researcher to fill out with the assistance of the recovery nurse. Participants will be day-stay cases and VAS pain will be recorded in the first hour post-operatively and every subsequent hour, for at least up to the third hour, until discharge.

Before the patient is discharged home, they will be given a physical pain diary along with their discharge summary and script for analgesia. The pain diary will include a VAS-pain to fill out at specified time points post-operation (at 8am and 6pm). Along with written and verbal instructions, patients will be notified with text reminders to fill the journal out. The written instructions will be on patients’ discharge summaries, pain diary, and dispensed medication box. VAS-pain recording will be made every day from postoperative day 1 (the day after surgery) to postoperative day 7. Twice daily recordings will be used to calculate daily and weekly averages of pain scores. All VAS pain scores are to be recorded for both pain at rest and movement.

|  |  |
| --- | --- |
| Hours post-op | VAS-P |
| 1 |  |
| 2 |  |
| 3 |  |
| 4, 5, 6+ etc (If still in hospital) |  |
| Week 1 (2 times a day for the week) |  |

Participants will be provided patient information leaflets detailing potential adverse effects of Diclofenac. If any adverse effects occur, participants are to report to nursing staff, who will inform the treating doctor/researcher. We predict side effects from a single preoperative dose of Diclofenac are unlikely to arise after discharge.

VAS pain score will be recorded on a 100mm line between two points with the left extreme being ‘no pain at all’ and the right being ‘worst pain possible’. Patients would make a mark on this line corresponding to their current level of the pain and the distance from the left extreme, ‘no pain at all’, to the distance on the mark will be measured to the nearest 1mm. The distance in mm will be the VAS pain score.

The minimal clinically important difference (MCID) of 15 mm for VAS pain scores will be used to determine the clinical significance of pain relief in the intervention group compared to the control group.

**Secondary outcomes:**

Secondary outcomes which focus on function, pain, and health related quality of life:

* Total Morphine Milligram Equivalent (MME) of additional postoperative opioid medications required for 1 week postoperatively (from postoperative day 0 to postoperative day 7)
* Lysholm at postoperative weeks 2 and 8
* KOOS-QoL at postoperative weeks 2 and 8
* Quality of recovery after anaesthesia (as per QoR-15 survey), recorded post-op day 1
* NRS for patient sleep, recorded for 1 week post-op

1 Week postoperatively:
Participants will record in the pain diaries the amount of pain relief medications they are taking per day from the moment they leave the operating theatre (in which they can receive support filling out from hospital staff) until postoperative day 7. Furthermore, participants will fill out a QoR-15 questionnaire on postoperative day 1 and NRS for sleep every day from postoperative day 1 to 7.

2 Week follow-up:

At two weeks post-operatively, patients will be scheduled into clinic where they can return their pain diaries. Whilst in the waiting room, patients will be provided a paper form to complete their Lysholm and KOOS-QoL questionnaire.

8 Week follow-up:
Patients will again return to clinic and as in the 2 week follow-up, will complete their Lysholm and KOOS-QoL questionnaire in the waiting room.

**Power Calculation**

The MCID is defined as the smallest change in a measurement that signifies an important improvement in a symptom. Using the mean change approach, MCID for VAS-pain in pain relief for a range of conditions, ranged from 8-40 mm, with a median of 17 mm [38]. Furthermore, Danoff et al determined the VAS-pain MCID to be 22.6mm for pain relief following TKA [39] whereas Laigaard et al found the median MCIDs for pain scores following total hip or knee arthroplasty to be 15mm at rest and 18 mm during movement.[40] The VAS-pain MCID is dependent on the type of procedure performed [39], however there is nothing in the literature to suggest a VAS-pain MCID for ACLRs.

To reduce the risk of a type 2 error, we have decided to power the study to detect a 15mm difference in VAS-pain at 1 hour post op, with an expected standard deviation of 20mm based on previous studies mentioned above. With a power of 80% and α = 0.05 this gives a total of 28 patients per group. 30 patients will be recruited in each group to account for any loss of follow-up, although based on our previous study in TKA we expect the loss to follow up to be minimal.

**Data Capture and Analysis**

Data will be recorded on Case Report Forms (CRFs; includes patient pain diaries). An investigator will complete and sign forms once they are completed by patients. The data will then be entered onto a secure excel spreadsheet by a research assistant. The original paper CRFs are to be stored securely, and archiving to be undertaken in accordance with ICH/GCP guidelines.

Means, standard deviation, and 95% confidence intervals will be calculated for the participant VAS-pain scores at each recorded time interval as the primary objective of the study. A general linear model or generalised linear mixed model, followed by independent two-sample t-test or Wilcoxon non-parametric rank sum test will be used to analyse the data. VAS-pain scores will be pooled according to the appropriate study group for comparison between the study arms. An MCID of 15 mm will be used to determine a clinically important difference in pain management.

For secondary objectives, independent two-sample t-test or Wilcoxon non-parametric rank sum test will be used to compare means of MME, QoR-15, sleep, Lysholm, and KOOS-QoL scores between the intervention group and control group.

The intended statistical test used will be dependent on the distribution of the data collected. This will be determined by appropriate normality and homogeneity testing of the data. If requirements are not met, a transformation may be applied, which will likely be logarithmic. Adjustments will be made accordingly based on the data obtained.

Baseline characteristics and preoperative survey scores will be compared using a two sample t-test or Wilcoxon non-parametric rank sum test. Gender comparisons between the two study groups will be analysed using a two-way analysis of variance (ANOVA) or in the case of non-parametric testing, Kruskal-Wallis test.

Adverse events will be recorded separately and reviewed by investigators for relevance to the procedure/intervention as well as commonalities. Frequency and percent distributions will be presented in tabular form and logistic regression will be used for comparison of the study groups.

**Selection Criteria for Investigators/Sites**

* The investigator(s) participating in this study is(are) qualified Orthopaedic surgeon(s).
* Research assistants and study staff will be under the direction of the Principal investigator (PI).
* Conflicts of interest (including financial assistance from other parties) will be declared by investigators and research personnel before starting the trial.
* A list entailing any persons, their qualifications, and their roles relating to the trial, must be kept by the PI.
* Sites must have adequate facilities and trial staff, as well as demonstrate that adequate participant recruitment is likely possible.
* Investigators must provide the appropriate medical care for participants if an adverse event were to occur during or following the trial (that is deemed related to the trial).
* A favourable Ethics Committee endorsement of the trial protocol, as well as any information provided to participants, must be obtained prior to investigators commencing the trial.
* The investigator/institution shall permit trial-related monitoring, audits, ethics review, and regulatory inspections. Trial-related data/documents will be made accessible under these circumstances.
* The trial must be conducted according to the approved protocol. Any deviation from the protocol must be documented for later review.
* No deviation from the approved protocol may occur without review and endorsement from the Ethics Committee, unless necessary to prevent imminent harm to participants.
* Investigators must ensure participants have given informed, written consent, with a thorough understanding of all trial procedures and risks.

**Admittance of Patient**

Prior to enrolling participants or beginning the study, written approval from the Ethics Committee and Governance must be obtained by the investigator.

Each patient must be reviewed pre-operatively in accordance with the inclusion and exclusion criteria by the investigator.

Upon signing the consent form and patient information sheet, a patient will be identified as a participant within this clinical trial.

**Patient Accounting**

An informed consent log consisting of details (NHI number and initials) of patients linked with their study number, who have completed the consent form, will be kept by the investigator.

Clinical trial data will be regularly monitored throughout the trial. Any trends and adverse events will be noted during the process. Participant voluntary withdrawal or loss to follow-up will be documented on a Study Completion Form.

**Data Quality Assurance and Data Safety Committee**

CRFs will be reviewed by an investigator or designee to ensure completeness and adequate accuracy, as well as for evidence which may indicate patient risk. Any noted discrepancies will be resolved by the investigator or designee. Attempts will be made to obtain data if possible, where the data is incomplete.

The clinical research team will be responsible for monitoring the trial site to ensure compliance with the study protocol and capture of any data or complications not already documented. Data will also be verified from source documents. A Data Safety Committee has not yet been formed, but will be formed prior to beginning the study. This should comprise of the PI, a statistical advisor and a patient advocate to review the data and any adverse event forms.

**Management of Concurrent Events**

Concurrent Illness/Procedures

Where participants experience inter-current illnesses or adverse events, any required concurrent procedures or medications will not be restricted during the study. Given the demographics of patients receiving ACLR, it can reasonably be expected that this may occur.

Withdrawal from Study

All study participants will be advised that they may voluntarily withdraw from the study at any stage, for any reason, and they have no obligation to state their reasoning. This will not affect their medical care. Even so, efforts will be made to try to determine the reason for withdrawal. A written request detailing their desire to withdraw from the study may be requested by an investigator. For all participants lost to follow up, attempts to locate them will be documented.

Circumstances for which a patient would be determined as not continuing in the study:

* Completion/termination of study
* Death
* Concurrent illness
* Lost to follow-up
* Other

Investigators may also choose to withdraw participants if they are unable to continue participation in the study due to some condition unrelated to this study. For all participants who withdraw from the study, a Study Completion Form will be completed.

Emergency Unblinding

Unbinding of participant treatment allocation may be required in the case of an adverse event. In such cases, if deemed necessary by the principal investigator, the participant’s allocation may be unblinded by the principal investigator, or a designee.

 **Modification of Protocol**

Unless written approval from the applicable Ethics Committee has been obtained, there will be no major modifications made to this study protocol. Any deviations to this study protocol will be detailed on a Protocol Deviation Form as soon as identified. Notification to the applicable Ethics Committee will be made according to the Ethics Committee requirements.

**Definitions and Reporting of Adverse Events**

Definitions

Adverse Events:

* Any undesirable clinical occurrence in a subject, whether it is considered to be study medication related or not, that includes a clinical sign, symptom, or condition; and/or an observation of an unintended technical procedural error.

Expected:

* An adverse event is expected when the specificity and severity of the event is consistent with a complication that is not related to the study specific medications or procedural technique, but may be related to the surgical procedure

Unexpected:

* An adverse event is unexpected when the specificity or severity of an adverse event is not consistent with the standard. It refers to an adverse event that has not been observed before

Adverse Study Medication Event:

* A clinical sign, symptom or condition that is causally related to the product, administration of the product, or performance of the product.

Serious Adverse Event:

* Any untoward medical occurrence that:
	+ Results in death,
	+ Is life threatening,
	+ Requires inpatient hospitalisation or prolongation of hospitalisation,
	+ Results in persistent or significant disability/incapacity,
	+ May have caused a congenital anomaly/birth defect,
	+ Requires intervention to prevent permanent impairment or damage,
	+ Is a medically important event or reaction.

**Reporting of Events**

Adverse Events:

Any adverse event that occurs at any point in time from the beginning of the surgical procedure until either the participant is terminated from the study, or 7 days post-completion, should be recorded as follows:

* All information on general medical, operative, and study medication related complications (adverse events) will be documented on Case Report Forms.
* Information should include date of occurrence, description, severity, relationship to study medication, treatment, and date of resolution.
* The investigator will determine if the event is related to the study medication.
* Any adverse event in a study patient must be monitored until it has resolved or been considered non-clinically significant by the investigator.

Expected Events:

Should be reported to the principal investigator as soon as possible, but not later than five working days after the investigator first learns of the event.

Adverse Study Medication Events

Study staff will ensure that any adverse study medication events which occur will be documented and immediately reported to the principal investigator. They should also be reported to the reviewing Ethics Committee and institution as soon as possible, no later than fifteen working days after the investigator learns of the event. An evaluation of the adverse events will be conducted by the investigator. Following this, if it is determined that the adverse effect presents an unreasonable risk to participants, the trial will be terminated as soon as possible. Termination shall occur no later than five working days after the investigator makes the determination, and no later than fifteen working days after the investigator first receives notice of the adverse event.

Serious Adverse Events (SAEs)

Any adverse event considered to be serious in nature which occurs at any time point from signing of Informed Consent Form until either the patient is terminated from the study, or 7 days post-completion, should be recorded as follows:

* All SAEs should be reported immediately to the principal investigator no later than 24 hours after becoming aware of the event.
* This will be followed promptly by detailed, written reports.
* The investigator should comply with the applicable regulatory requirement(s) related to the reporting of serious unexpected adverse study medication reactions to the regulatory authority (MedSafe NZ) and the Ethics Committee.
* All other SAEs not related to the study medication will be reported to the Ethics Committee as directed.

**Ethics Committee**

Approval

The investigator is responsible for obtaining Ethics Committee and Governance approval to conduct this study

Prior to Initiation of the Study

Written approval by the Ethics Committee and Governance must be obtained prior to beginning the study. Discussions may be had with prospective participants regarding the study, however written Patient Informed Consent must not be obtained. Until all approvals are granted, study procedures must also not be performed on prospective study participants.

Progress Reports

Progress reports on the trial will be submitted by the investigator at the request of the Ethics Committee.

Final Reports

Upon completion of the investigation, each investigator will submit an Ethics Close-Out Report on his/her part of the investigation within three months of completion of the investigation. This will be submitted to the Ethics Committee.

**Use of Information and Publications**

Investigators will and must respect data confidentiality. The information obtained during this study will be used in publications and conferences. Anonymity of the participants will be maintained in dissemination.

**Analysis/Conclusions**

The data gathered in this investigation will be maintained and periodically assessed throughout the study. Given the above design and planned analysis, we believe this protocol is scientifically sound, and that clinical evaluation of the novel procedure is justified.

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