**HEALTH RESEARCH PROTOCOL**

**TEMPLATE FOR CLINICAL TRIALS**

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| **1. Trial Details** |

* 1. Trial Details.

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| **Protocol/Clinical Trial Title:** | Ultrasound guided hamstring block to reduce autologous graft site pain in hamstring tendon anterior cruciate ligament reconstruction  |
| **Protocol Number (Version and Date):** | Ver 4 20 NOV 19 |
| **Amendment** **(Number and Date):** |  |
| **Trial Start Date:** | February 2020 | **Trial Finish Date:** | February 2021 |
| **Coordinating Principal Investigator Name:** | Dr Hamish Mace |
| **Coordinating Principal Investigator Contact Details:** | Hamish.mace@health.wa.gov.au |
| **Sponsor Name (if applicable):** | N/A |
| **Laboratory Name (if applicable):** | N/A |

* 1. Trial Summary (less than 300 words) including background, objectives and trial plan.

***Trial Objective***

To determine the efficacy of the ultrasound guided “hamstrings block” in reducing pain and enhancing quality of recovery following anterior cruciate ligament reconstruction (ACLR) with a hamstring autograft.

***Background***

The anterior cruciate ligament (ACL) is the most frequently injured ligament of the knee with the incidence of ACL reconstruction (ACLR) increasing [1]. The arthroscopic operation is usually performed on a young and sporting population with patient satisfaction primarily related to return to pre-injury function[2]. Optimisation of a peri-operative analgesic regime enhances recovery and post-operative rehabilitation [3] and enables surgery on an ambulatory basis but inadequate analgesia is a primary cause for failed discharge [4].

An autologous tendon graft is often utilised to reconstruct the injured ACL with both a bone-patella tendon-bone and four-strand hamstring tendon as equally viable sources [5]. Consensus guidelines on regional analgesia were published by the Society for Ambulatory Anaesthesia in 2019 [6]. These were largely based on literature where bone-tendon-bone grafts were used in the majority of studies and cannot be generalised to techniques where a hamstring graft is utilised [7] as donor site pain from graft harvest is a significant contributor to post-operative pain [8]. Limited techniques for local infiltration or regional anaesthesia have been previously described; direct injection of local anaesthetic along the operative site [8, 9] or injection through an arthroscopic shaver [10]. Description and proven efficacy of an ultrasound guided hamstrings block will provide another alternative analgesic regime that improves post-operative analgesia, preserves mobility and enables early ambulation leading to same day discharge.

***Trial Plan***

* Literature review of current ACLR analgesia regimes
* Anatomical and ultrasound description of hamstrings block as described by Hebbard
* Multicentre single blinded randomised control trial – patients undergoing ACLR will be randomised to standard care (general anaesthesia, multimodal analgesia and adductor canal block) or standard care with an ultrasound guided hamstrings block
* Primary outcome of quality of post-operative analgesia with secondary outcome of quality of recovery
* Analysis of results
* Peer reviewed publication of results in 12 months

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| **2. Rationale / Background** |

2.1

Although the arthroscopic nature of the surgery is minimally invasive, there is significant potential for post-operative pain that requires a careful consideration of multimodal analgesic regime. Opioid analgesia remains the mainstay of treatment of severe post-operative pain but reducing opiate consumption following surgery can lead to improvements in a patient’s functional recovery and reduce systemic side effects caused by drug therapy. These concepts are especially important in an era where the complications of opioid therapy are increasingly being recognized [11,]12].

Numerous peripheral nerve block techniques as adjuncts for controlling post-operative ACLR pain have been trialled [7, 13, 14]. The knee receives innervation from the femoral/saphenous nerve and sciatic nerve, with a variable contribution from the obturator nerve [15]. The femoral, saphenous and sciatic nerves can be blocked through well recognised ultrasound or nerve stimulator guided techniques. This typically involves injecting long-acting amino-amide local anaesthetic agents such as bupivacaine or ropivacaine, in addition to adjuncts such as adrenaline, clonidine or dexamethasone to the appropriate anatomical site. These agents provide intraoperative anaesthesia and analgesia of the affected nerve distribution, with analgesic effects continuing for up to 24 hours [16]. The aim of a peripheral nerve block is to provide maximum sensory blockade of the knee joint to aid analgesia whilst minimising motor blockade that would reduce limb power and inhibit mobilisation and rehabilitation post operatively. The analgesic effect of performing these blocks also needs to be balanced against the general nerve block complications that include vascular injury, persisting neural injury and systemic local anaesthetic toxicity.

The adductor canal block, whereby local anaesthetic is deposited distal to the femoral triangle and deep to Sartorius muscle is useful for ACLR as it provides good analgesia without any direct resultant motor weakness [17]. Adductor canal block will not cover hamstring graft pain due to the tendons differing innervation. The hamstrings block will anaesthetise the terminal muscular fibres which innervate the tendinous hamstring graft and so obviate the need for blockade of the sciatic nerve for the hamstrings donor graft site. Sciatic nerve blockade leads to moderate to severe motor weakness in the form a foot drop and thus ambulation is significantly impaired. Additionally, it may be a safer technique as there is no risk of neuropraxia as when blocking a major peripheral nerve. The ultrasound guided hamstrings block is being currently being performed as an additional block to cover the hamstring donor graft harvest site. However, the ultrasound guided hamstrings block is yet to be described in the peer reviewed literature and a trial of efficacy has not been conducted.

2.2 Name and description of the intervention or product(s) used in this trial, including investigational product(s) and comparator product/s (if applicable). Include status of product registration

The ultrasound guided hamstrings block was developed by Hebbard (https://peterhebbard.com/hamstrings-block.html) following anatomical and ultrasound studies which sought to derive improved analgesia for patients undergoing hamstring ACLR. It involves the injection of local anaesthesia deep to the gracilis muscle (which takes its innervation from the obturator nerve) between the gracilis and adductor magnus muscle, and deep to the semimembranosus muscle (which is innervated by the sciatic nerve) between the semimembranosus and semitendinosus. The local anaesthetic is placed under ultrasound guidance.

The hamstring block will be performed with ultrasound guidance using a 100mm 22g *Stimuplex* needle to inject:

* + - 20ml 0.2% Ropivacaine (40mg Ropivacaine) with placed posterior to the belly of gracilis at the level of the adductor canal (mid-thigh)
		- 20ml 0.2% Ropivacaine (40mg Ropivacaine) is placed either side of semitendinosus in the mid-thigh

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| **3. Trial Aims / Objectives / Hypotheses** |

* 1. Detailed description of the specific primary and secondary objectives and the purpose of the trial. Describe any hypotheses that will be tested.

**Key Research Question**

Is the ultrasound guided 'hamstring block' an effective additive to adductor canal blockade following autologous hamstring ACL reconstruction?

**Null Hypothesis to be Tested**

An ultrasound guided “hamstrings block” in addition to an adductor canal block does not significantly reduce oral morphine equivalents consumption following anterior cruciate ligament reconstruction in the 24 hour post-operative period.

*Primary Objective*

* To explore whether an ultrasound guided “hamstrings block” can reduce the analgesia requirement following ACLR

Secondary Objectives

* To explore whether an ultrasound guided “hamstrings block” can improve quality of recovery following an ACLR
* To explore whether an ultrasound guided “hamstrings block” causes inadvertent sciatic nerve blockade

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| **4. Trial Design** |

***The scientific integrity of the trial and the credibility of the trial data depend substantially on the trial design and methodology.***

* 1. Primary endpoints and the secondary endpoints, if any, to be measured during the trial and how they will be measured.

All data will be collected on the case report form attached.

**Primary Endpoint**

* Total Oral Morphine Equivalent Consumption 24 Hours Post Operatively – prescription and recovery analgesia charts will be retrospectively reviewed and all analgesic medications consumed recorded on the case report form. Post discharge analgesia consumed reported by the study participants during a post-operative follow up phone call will be also recorded on the form. The total analgesia consumed in the first 24 hours (from arrival in PACU) will then be converted to oral morphine equivalents. Oral morphine equivalents will be calculated using standardised tables published by the Australia New Zealand College of Anaesthetists “Opioid Dose Equivalence” charts (<https://fpm.anzca.edu.au/documents/opioid-dose-equivalence.pdf>). Comparison of the patient’s analgesic consumption into an oral morphine equivalents will enable a quantitative comparison of analgesic efficacy in the control versus the study group. Oral morphine equivalent consumption is a well-recognised and utilised research tool to examine the effects of analgesic regimes where there is a decrease in consumption with more effective analgesia.

**Secondary Endpoints**

The secondary endpoints for this study will be divided into pain related objectives and function related objectives.

*Pain Related End Points*

* Numerical pain rating scores – researchers or nurses directly caring for the study participants will ask them for a numerical pain rating score (0 to 10) in the post anaesthetic care unit immediately following emergence from anaesthesia and then at 1 hour, 6 hour and 24 hour post-operatively. At 6 hour and 24 hour post-operative marks, both resting and dynamic pain scores will be recorded.
* Time to first opioid dose – the time of arrival in the post anaesthetic care unit will be noted. Either the time to first opioid administration will be noted or retrospectively reviewed and the difference of times calculated.
* Presence of post-operative nausea or vomiting – the presence of nausea or vomiting that requires anti emetic administration will be recorded immediately post operatively, 1 hour, 6 hour and 24 hour post operatively.
* Presence of saphenous nerve blockade – blockade of the sensory nerve will be examined for by clinical examination. This will be tested by reduced sensation to ice on the medial malleolus of the ankle of the operative/blocked side compared to the non-operative side. If there is a difference then a sensory blockade will be recorded as yes. This will signify that an effective adductor canal block has been placed.
* Presence of sciatic nerve motor blockade – blockade of the sensory and motor components will be examined for by clinical examination.
	+ Sensory blockade will be tested by reduced sensation of ice on the lateral side of the foot of the operative/blocked side compared to the non-operative side. If there is a difference then sensory blockade will be recorded as yes.
	+ Motor blockade will be tested by power of the extensor hallucus longus, with comparison to the non-operative side. If there is a difference then motor blockade will be recorded as yes.

*Function Related End Points*

* Quality of Recovery 15 Score – the quality of recovery score is a validated score to evaluate how well patients recover following surgical procedures. This will be conducted by researchers pre-operatively and at 24 hours post operatively over the phone.
	1. Type (e.g. phase, pilot) and design (e.g. double-blind, placebo-controlled, parallel design) of the trial to be conducted and a schematic diagram of the trial design, procedures and stages (e.g. initial assessment, run-in, pre-randomisation assessment, randomisation, treatment phase, end-of-treatment assessment, washout, cross-over, alternative treatment, post-treatment assessments, trial exit).

This phase III trial is a single blinded randomised control trial of a novel ultrasound guided hamstrings block in patients presenting for elective anterior cruciate ligament reconstruction.

Assessed for eligibility

## Follow Up

**Record Data**

 Lost to follow up

 Primary and secondary end points

**Record Data**

 Lost to follow up

 Primary and secondary end points

## Enrollment

**Allocated to Control Group**

 Received allocated intervention

 Did not receive allocated intervention

## Allocation

**Allocated to Intervention Group**

 Received allocated intervention

 Did not receive allocated intervention

Excluded

  Not meeting inclusion criteria

  Meeting exclusion criteria

  Declined to participate

## Assessment

Pre Randomisation Assessment and Consent

Randomized

## Analysis

## Trial Exit

**Enrolment**

*Inclusion criteria*

1. Patients undergoing ACL reconstruction with ipsilateral hamstrings graft
2. Age between 18 and 65
3. Operation performed under general anaesthesia

*Exclusion criteria*

1. Patients having ACLR without hamstrings graft
	1. ACL reconstruction using unilateral or contralateral patellar / quadriceps tendon grafts
	2. ACL reconstruction using allogenic (deceased donor) grafts
	3. ACL reconstruction with multi-ligament repair
2. Contralateral graft harvest site
3. Revision surgery
4. Allergy to amide local anaesthetic or its constituents
5. Allergy or contraindication to the administration of the adjuvant analgesic agents
6. Chronic pre-operative opioid use (>30mg oral morphine equivalent daily)
7. Hepatic or renal insufficiency
8. Patients unable or unwilling to give consent
9. Pregnancy
10. Spinal anaesthesia
11. Intra operative fentanyl dose greater than 4 mcg/kg
12. Pre-operative analgesia
13. Use of intraoperative nitrous oxide
14. Use of surgical instilled local anaesthetic into the hamstring donor site

**Assessment**

* Patient Demographics will be recorded – Age, Weight, ASA score, gender

**Randomisation**

* Patients will be randomized to the control or intervention group based on an online randomisation website which each researcher can access.

**Follow Up**

* Surgical Data
	1. Meniscal resection or repair
	2. Graft adjunct (lars, allograft, etc.)
	3. Type of tunnel
	4. Graft Source
	5. Surgical time
	6. Tourniquet Time
* Pain Data
	1. Total oral morphine equivalent 24h dose
	2. Numerical pain scores (0-10) at time 0h, 1h, 6h and 24h post-operative
	3. Time to administration of opiate analgesia
	4. Presence of post-operative nausea and vomiting requiring antiemetics (Y/N) at time 0h, 1h, 6h and 24h post-operative
	5. Presence of sciatic nerve motor blockage (Y/N) at time 0h
* Functional Data
	1. QOR15 questionnaire pre-operatively and at 24 h post operatively
* Length of stay

**Analysis**

Demographics will be presented as number (percent) for discrete variables and median (interquartile range) for continuous variables. Tests between study group will be completed using two-tailed approaches, with p < 0.05 defined as the threshold for rejection of the null-hypothesis. Standard testing for normality (Shapiro-Wilk) will be completed to determine if parametric or non-parametric testing strategies are most appropriate for the analysis of the data in question. If cross over occurs between the placebo and active treatment groups, the patient data will be included in the group to which randomisation occurred (intention to treat analysis).

* 1. Measures taken to minimise/avoid bias, including randomisation and blinding.

Study participants will be randomised to either the control or to the intervention group by a randomisation website. Post-operative follow-up will be by a different researcher whom will be blinded to the group allocation and whom was not involved in the intra-operative care of the patient (single blinded).

To minimise bias during follow-up, a standard dressing will be placed at the insertion site of the hamstrings block in both the intervention and control group. This will aim to remove the visual clue of whether the hamstrings block has been performed or not to both the patient and researchers.

* 1. Maintenance of any blinding records or randomisation codes and procedures for breaking codes.

Each patient recruited to the study will be randomised to the control or study group by a randomisation website. Patients will be allocated a study number that will be linked to their group allocation on a computer spreadsheet. Group allocation will not be released to the researchers until recruitment has been completed. If a group allocation needs to be revealed prior to completion of the study, the principal investigator can be contacted and the code obtained.

* 1. Method of tracking implantable devices (if applicable)

Not applicable

* 1. A description of the interventions or investigational product(s). For drug trials information regarding the dosage and dosage regimen, as well as a description of the dosage form, packaging, dispensing and labelling should be included.

A detailed description of the intervention is within methods 2.2.

* 1. Accountability procedures for the investigational product(s) including the placebo(s) and comparator(s) (if applicable).

The comparator control group study participants will receive the current standard of practice for their peri-operative analgesic regime that is currently being administered by the researchers for patients whom present for ACLR. They will not receive the additional ultrasound guided “hamstrings block” that is being studied.

* 1. Expected duration of the trial and participant participation, including a description of the sequence and duration of all techniques or assessments to be performed, including follow-up (e.g. interventions, procedures, measurements, observations, laboratory investigations). Provide a schedule of assessments in a table if possible.

***Trial Dates***

Start Date: January 2020

End Date: January 2021

***Participant Participation***

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| **Phase** | **Expected Duration** | **Comments** |
| Assessment (pre-operative) | 10 minutes | Eligibility assessment, consent, demographic measures (Age, Weight, ASA score, gender) and Quality of Recovery Score 15 questionnaire  |
| Intervention (intra operative) | 15 minutes | Perform ultrasound guided “hamstrings block” under general anaesthesia if allocated to intervention group |
| Follow Up (24 hours post-operative) | 10 minutes | Most of the data will be recorded during the routine post-operative stay and no extra time is required. One phone call will be received on the first post-operative day to obtain analgesic consumption and quality of recovery score 15 which will take approximately 5 minutes and would be regarded as good clinical practice. * Pain Data
	1. Total oral morphine equivalent 24h dose
	2. Visual analogue pain scores (0-10) at time 0h, 1h, 6h and 24h post-operative
	3. Time to administration of opiate analgesia
	4. Presence of post-operative nausea and vomiting (Y/N) at time 0h, 1h, 6h and 24h post-operative
	5. Presence of sciatic nerve motor blockage (Y/N) in PACU.
* Functional Data
	1. QOR15 questionnaire pre-operatively and at 24 h post operatively
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* 1. Criteria for the termination of the trial. Description of the discontinuation criteria for individual participants, parts of the trial and entire trial.
* Discontinuation criteria for individual patients – change of surgical or anaesthetic technique to meet exclusion criteria, request to leave the trial
* Discontinuation criteria for parts of the trial – not applicable
* Discontinuation criteria for entire trial – major adverse event noted that is attributed to ultrasound guided “hamstrings block”
	1. The identification of any data to be recorded directly on the Case Report Forms (CRFs) (i.e. no prior written or electronic record of data), and to be considered to be source data.

Participants will be allocated a study number, which will be used to identify images and study related data. The patient details and number allocation will be securely stored in a locked filing cabinet or a password-protected computer within the anaesthetic research department. No information that could identify participants will be used in the final paper.

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| **5. Source and Selection of Participants** |

* 1. Source of participants - research population, sample size, source, and sampling frame (if possible, split by site if multicentre trial).
* Research population – elective patients presenting for anterior cruciate ligament reconstruction
* Sample size – 88 patients
* Sampling frame
	+ Fiona Stanley Hospital – 8 patients
	+ Fremantle Hospital – 40 patients
	+ Osborne Park Hospital – 10 patients
	+ Sir Charles Gairdner Hospital – 10 patients
	+ Mercy Ascot group hospitals, Southern Cross Healthcare hospitals and Ormiston Hospital– 20 patients
	1. Participant inclusion criteria. Describe appropriate criteria for special risk populations (e.g. women of reproductive age, participants with disease states or organ impairment).

*Inclusion criteria*

1. Patients undergoing ACL reconstruction with ipsilateral hamstrings graft
2. Aged between 18 and 65
3. Operation performed under general anaesthesia
	1. Participant exclusion criteria. May include conditions that increase the risk to the participant, that interfere with the participants ability to give informed consent or interfere with a participant’s ability to comply.

*Exclusion criteria*

1. Patients having ACLR without hamstrings graft
	1. ACL reconstruction using unilateral or contralateral patellar / quadriceps tendon grafts
	2. ACL reconstruction using allogenic (deceased donor) grafts
	3. ACL reconstruction with multi-ligament repair
2. Contralateral graft harvest site
3. Surgical local anaesthetic infiltration
4. Revision surgery
5. Allergy to amide local anaesthetic or its constituents
6. Allergy or contraindication to the administration of the adjuvant analgesic agents
7. Chronic pre-operative opioid use (>30mg oral morphine equivalent daily)
8. Hepatic or renal insufficiency
9. Patients unable or unwilling to give consent
10. Pregnancy
11. Spinal anaesthesia
12. Intra operative fentanyl dose greater than 4 mcg/kg
13. Pre-operative analgesia
14. Use of intraoperative nitrous oxide
	1. Participant withdrawal criteria (i.e. terminating investigational product/trial treatment) and procedures specifying:

(a) when and how to withdraw participants from the investigational product/trial treatment;

(b) the type and timing of the data to be collected for withdrawn participant(s);

(c) whether and how participants are to be replaced; and

(d) the follow-up for participants withdrawn from the investigational product/trial treatment.

* Participants can withdraw from the trial at any stage by informing a researcher or contacting the principal investigator in person, by phone or email
* Withdrawn participants will have no further data collected
* Participants who withdraw will be replaced by continued recruitment into the study
* In the event that a participant withdraws from the study, (excepting in circumstances in which the safety of the technique requires review, whereupon the study will be paused or terminated, as appropriate); an additional participant will be recruited to ensure adequate power.
* Follow up of participants whom withdraw will be followed up as clinically indicated

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| **6. Treatment of Participants** |

* 1. Description and justification for the treatments, interventions or methods to be utilised (including product name(s), dose(s), dosing schedule(s), route/mode(s) of administration and treatment period(s)) and the follow-up period(s) for participants for each investigational product/trial treatment group/arm of the trial.

Following informed consent for inclusion in the study, subjects will receive a standard general anaesthetic with routine monitoring. The anaesthetic regime described below would be regarded as a good standard of care for patients undergoing ACLR.

Induction of anaesthesia will be performed with 1-2mcg/kg of fentanyl and propofol titrated to effect. Anaesthesia will be maintained with sevoflurane in air: oxygen to achieve an age adjusted MAC (minimum alveolar concentration) of 1.0. An Fi02 of 0.5 will be administered and ventilation managed to achieve tidal volumes of 7-10ml/kg prior to the establishment of spontaneous ventilation. Ventilation will be either spontaneous or pressure supported and fentanyl will be titrated to achieve a respiratory rate of 10-16/min.

* Pre-Operative – no premedication’s will be given
* Blocks:
	+ Standard Care - adductor canal block will be placed via ultrasound guidance with 20ml 0.2% ropivacaine (40mg Ropivacaine) distal to the femoral triangle and deep to sartorius muscle using a 100mm 22g *Stimuplex* needle.
	+ Standard Care Plus Hamstring block – in addition to adductor canal block above a hamstring block will be performed via ultrasound guidance using the same 100mm 22g *Stimuplex* needle to inject:
		- 20ml 0.2% Ropivacaine (40mg Ropivacaine) with placed posterior to the belly of gracilis at the level of the adductor canal (mid-thigh)
		- 20ml 0.2% Ropivacaine (40mg Ropivacaine) is placed either side of semitendinosus in the mid-thigh

Blocks will be performed after general anaesthesia has been established. Blocks will be performed by consultant anaesthetists or regional anaesthesia fellows under direct supervision.

* Intra Operative medications - parecoxib 40mg, paracetamol 1g iv, ondansetron 4mg iv, dexamethasone 4mg iv, fentanyl titrated to respiratory rate of 10 to 16 up to maximum of 4 mcg/kg,
* Local Anaesthetic by Surgeons = both groups will receive a standard 50mls of 0.2% Ropivacaine (100mg Ropivacaine) that will be instilled in the pre tibial region or within the joint capsule and not within the hamstrings donor site by the surgical team.
* Post anaesthetic care unit – intravenous morphine (nurse titrated), cyclizine 25-50mg iv,
* Ward - 50 to 100mg IR Tramadol up to 600mg in 24 hours and availability of oral opiate analgesia (morphine or oxycodone), ondansetron 4-8mg tds iv
* Discharge medication – oral tramadol 50mg tds prn, oral oxycodone or morphine prn

Follow up of patients will begin immediately in the post-operative period and be complete by 24 hours post operatively.

* 1. The medications/treatments permitted (including rescue medication) and not permitted before and/or during the trial.

All medications mentioned above will be permitted before/during and after the trial

* 1. The procedures for monitoring participant compliance.

Not applicable.

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| **7. Assessment of Efficacy** |

* 1. Specification of the efficacy parameters.
1. To explore whether an ultrasound guided “hamstrings block” can reduce the analgesia requirement following ACLR
2. To explore whether an ultrasound guided “hamstrings block” causes inadvertent sciatic nerve blockade
3. To explore whether an ultrasound guided “hamstrings block” can improve quality of recovery following an ACLR
	1. The methods and timing for assessing, recording, and analysing efficacy parameters.
4. This will be assessed using 24-hour opiate consumption, pain scores post operatively
5. This will be specifically tested for post operatively by clinical examination
6. This will be assess using a pre and post-operative quality of recovery score 15 (validated measure of quality of recovery)

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| **8. Assessment of Safety** |

* 1. Summary of known and potential risks and benefits, if any, to research participants.

**Risks**

Ultrasound guided nerve blocks are commonly performed as part of a peri-operative regional anaesthetic regime. Ultrasound is a non-invasive and safe method of imaging. The additional “hamstrings block” will be performed either by consultant anaesthetist with an interest in regional anaesthesia or regional anaesthesia fellow directly supervised by such a consultant. The dose of local anaesthetic in total for each patient will not exceed the recommended threshold of toxicity of Ropivacaine of 3mg/kg (240mg for an 80kg adult). Nerve blocks will be conducted in standard aseptic technique to prevent infection. As no nerve is being blocked directly, the risk of neuropraxia is remote, yet not impossible. Other risks applicable to all nerve blocks would include inadvertent intravascular injection, bleeding, haematoma, failure of the block. Given the anatomy of the hamstrings block being studied these risks would also be regarded as relative to other blocks commonly performed. Local anaesthetic systemic toxicity is another considered risk whilst performing nerve blocks but good technique and keeping the total dose of Ropivacaine under the recommended 3mg/kg will mitigate this risk as well as the systemic uptake from the relatively avascular hamstrings donor site being regarded as low.

**Benefits**

Potential benefits to the participant are improved analgesia after the operation and thus a reduced requirement for oral or intravenous analgesia, with concomitant reduced side effects. Improved analgesia may also lead to an improved functional quality of recovery and earlier rehabilitation. Participants may also find participation in research intrinsically interesting and value the opportunity to contribute to a study that may improve the treatment of others.

* 1. The safety parameters and the methods and timing for assessing, recording, and analysing safety parameters. Include a description of emergency procedures if applicable.
* Safe dose of Ropivacaine – total dose of Ropivacaine local anaesthetic will not to exceed 3mg/kg
* Emergency procedures – local anaesthetic systemic toxicity will be managed as per standard ANZCA crisis management.
	1. Details of the Data and Safety Monitoring Board, or equivalent.
	2. The procedures for eliciting reports of and for recording and reporting adverse events. Include definitions of adverse events.

All serious adverse event will be reported to the trial data and safety monitoring committee (to be established) and through the relevant hospitals adverse event monitoring system / committee. Following adjudication by the trial data and safety monitoring committee a decision will be made in consultation with the primary investigator and the anaesthetist treating the patient in question as to the appropriate course of action. This may include pausing of the study to allow for additional investigations or referral to an appropriate specialist for additional management.

* 1. The type and duration of the follow-up of participants after adverse events.

Follow up with participants after adverse events will be as per good clinical practice guidelines. Appropriate specialist referrals will be made as required. All paper and electronic trial records will be kept for at least 10 years in a locked filing cabinet or on a password protected secure hospital computer server at the Department of Anaesthesia and Pain Medicine at Middlemore Hospital as per the relevant legislation.

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| **9. Data Management, Statistical Analysis and Record Keeping** |

* 1. Description of the statistical methods to be employed, including timing of any planned interim analysis.

Demographics will be presented as number (percent) for discrete variables and median (interquartile range) for continuous variables. Tests between study group will be completed using two-tailed approaches, with p < 0.05 defined as the threshold for rejection of the null-hypothesis. Standard testing for normality (Shapiro-Wilk) will be completed to determine if parametric or non-parametric testing strategies are most appropriate for the analysis of the data in question. No interim analysis is planned.

* 1. The number of participants planned to be enrolled (if possible, include number at each site). Document the reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

A sample size has been calculated by retrospective analysis of 50 consecutive patients across the two of the study sites (Mount Hospital, Mercy Ascot Hospital). The mean opioid consumption (IV morphine equivalent) during the duration of the patient’s hospital admission was 48.5 mg (Standard Deviation 21.8mg). Using α = 0.05 with two tailed approach to statistical tests, β = 0.20 and power = 0.80 with one to one enrolment between the placebo and active hamstring block groups, 40 patients will be required in each group to detect a 10mg iv morphine/30mg oral morphine equivalent reduction between the intervention and control group. A reduction in 10mg iv morphine/30mg oral morphine consumption would demonstrate a clinically significant difference. We propose to recruit 40 + 10% patients in each group to allow for changes in surgical decision making and patient drop-out after randomisation has occurred.

* 1. The level of significance to be used.

A p value of 0.05 will be used (two tailed)

* 1. Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).

If cross over occurs between the control and intervention groups, the patient data will be included in the group to which randomisation occurred (intention to treat analysis). All deviations from the original statistical plan will be reported and justified.

* 1. The selection of participants to be included in the analyses (e.g. all randomised participants, all dosed participants, all eligible participants, or all evaluable participants).

Patients will be included if they underwent anterior cruciate ligament reconstruction with an autologous hamstring tendon graft.

* 1. Information on how data will be managed, including coding for computer analysis and data handling (collection, storage, maintenance, security and archiving). Include details regarding these processes if the data is sent off-site (e.g. encryption). *Clinical trial records should be retained for a minimum of 15 years from the completion of the trial.*

Participant data will be securely stored on a password-protected computer within the anaesthetic research department at Counties Manukau Health - Middlemore Hospital. Data collection sheets and hard copies of data collected will be stored in a secured filing cabinet (In the anaesthetic research department at Counties Manukau Health - Middlemore Hospital) and destroyed after 10 years.

* 1. Procedure for accounting for missing, unused, and spurious (*false*) data.

If a block is unable to be performed leading to no data being collected; an additional participant will be recruited to ensure that the study is sufficiently powered. Spurious data will be scrutinised on a case-by-case basis. Whilst it is common practice to exclude, for instance, outliers that meet a priori criteria: in this particular study, given inter-individual variation in human anatomy and physiology, ‘unusual data’ may arise from a number of sources and will be scrutinised by a panel of experts to determine its validity

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| **10. Monitoring / Audit** |

* 1. Statement that the trial investigators/institutions will permit trial-related monitoring, audits, and regulatory inspections, providing direct access to source data/documents. This may include, but not limited to, review by external sponsors, Human Research Ethics Committees and institutional governance review bodies.

The investigators will allow trial-related monitoring, audits and regulatory inspections and will allow direct access to all necessary data.

* 1. Description of the procedures for monitoring and auditing. *The clinical trial sponsor may nominate the form of monitoring and auditing and will indicate the times of audit visits.*

As the study can be audited, participant consent forms will be stored in a locked filing cabinet in the anaesthetic research office. Data will be kept in an appropriately labelled database on the anaesthetics research drive at Counties Manukau Health - Middlemore Hospital. By following the trials standard operating procedures, a secure audit trail will be maintained.

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| **11. Quality Control and Quality Assurance** |

* 1. Statement that the trial will be conducted in compliance with the protocol, Good Clinical Practice and the application regulatory requirements.

This trial will be conducted in compliance with the protocol, Good Clinical Practice and the application regulatory requirements

* 1. Quality control & quality assurance measures to ensure quality of data.

The research team will follow the standard operating procedures to ensure that data collected are reliable and valid. We will strive to ensure a full data set and maximum follow up.

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| **12. Ethics** |

* 1. Description of ethical considerations related to the trial with particular reference to participant consent (including Participant Information and Consent Forms).

Particular consideration has been given in this trial to the potential for coercion, given that the participants will be first and foremost patients of the research team. As such, arrangements will be made, where possible, to discuss enrolment into the study with a person whom is not the primary anaesthetist and facilitate delivery of the participant information sheet well before the procedure. Both the participant information sheet and consent form are included in this application.

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| **13. Budget, Financing, Indemnity and Insurance** |

* 1. Budget, financing, indemnity and insurance, if not addressed in a separate agreement.

See site-specific approval form.

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| **14. Publication**  |

* 1. Publication and dissemination of trial results (including any limitations), if not addressed in a separate agreement. *In accordance with the Declaration of Helsinki (2008) every clinical trial must be registered in a publicly accessible database before recruitment of the first participant*
	2. Results will be disseminated to specialists via local and international meetings and published in a peer-reviewed journal.

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| **15. References** |

* 1. A list of articles from the literature pertinent to the evaluation of the trial. Include references that have been cited in the protocol.

1. Herzog, M.M., et al., *Trends in Incidence of ACL Reconstruction and Concomitant Procedures Among Commercially Insured Individuals in the United States, 2002-2014.* Sports Health, 2018. **10**(6): p. 523-531.

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3. Lentz, T.A., et al., *Factors associated with function after anterior cruciate ligament reconstruction.* Sports Health, 2009. **1**(1): p. 47-53.

4. Andres-Cano, P., et al., *Postoperative complications of anterior cruciate ligament reconstruction after ambulatory surgery.* Rev Esp Cir Ortop Traumatol, 2015. **59**(3): p. 157-64.

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6. Abdallah, F.W., et al., *Pain Management for Ambulatory Arthroscopic Anterior Cruciate Ligament Reconstruction: Evidence-Based Recommendations From the Society for Ambulatory Anesthesia.* Anesth Analg, 2019. **128**(4): p. 631-640.

7. Yung, E.M., et al., *Evidence Basis for Regional Anesthesia in Ambulatory Anterior Cruciate Ligament Reconstruction: Part III: Local Instillation Analgesia-A Systematic Review and Meta-analysis.* Anesth Analg, 2019. **128**(3): p. 426-437.

8. Sonnery-Cottet, B., et al., *Analgesia after ACL reconstruction: Hamstring donor-site injection versus intra-articular local anaesthetic injection.* Orthop Traumatol Surg Res, 2017. **103**(2): p. 235-238.

9. Fauno, P., et al., *Analgesic effect of hamstring block after anterior cruciate ligament reconstruction compared with placebo: a prospective randomized trial.* Arthroscopy, 2015. **31**(1): p. 63-8.

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11. Wojcikiewicz, T. and K. El-Boghdadly, *Analgesic strategies for day-case knee surgery.* Anaesthesia, 2019. **74**(4): p. 529-533.

12. Anthony, C.A., et al., *Opioid Demand Before and After Anterior Cruciate Ligament Reconstruction.* Am J Sports Med, 2017. **45**(13): p. 3098-3103.

13. Vorobeichik, L., et al., *Evidence Basis for Regional Anesthesia in Ambulatory Anterior Cruciate Ligament Reconstruction: Part I-Femoral Nerve Block.* Anesth Analg, 2019. **128**(1): p. 58-65.

14. Sehmbi, H., et al., *Evidence Basis for Regional Anesthesia in Ambulatory Arthroscopic Knee Surgery and Anterior Cruciate Ligament Reconstruction: Part II: Adductor Canal Nerve Block-A Systematic Review and Meta-analysis.* Anesth Analg, 2019. **128**(2): p. 223-238.

15. Hong, A.J., et al., *Neurological structures and mediators of pain sensation in anterior cruciate ligament reconstruction.* Ann Anat, 2019. **225**: p. 28-32.

16. Secrist, E.S., et al., *Pain Management After Outpatient Anterior Cruciate Ligament Reconstruction: A Systematic Review of Randomized Controlled Trials.* Am J Sports Med, 2016. **44**(9): p. 2435-47.

17. Abdallah, F.W., et al., *Adductor Canal Block Provides Noninferior Analgesia and Superior Quadriceps Strength Compared with Femoral Nerve Block in Anterior Cruciate Ligament Reconstruction.* Anesthesiology, 2016. **124**(5): p. 1053-64.

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| **16. Appendices**  |

* 1. List all appendices. Including an Investigator’s Brochure or Device Manual (if applicable). *All trials involving unregistered drugs must be accompanied by an investigator’s brochure which is a compilation of the clinical and non-clinical data available on the experimental products intended for use in the trial. Clinical investigations involving devices should include an Investigator’s Brochure or Device Manual.*