University of Sheffield

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

NHS
National Institute for Health Research

Pain Relief After Instrumented Spinal surgEry trial (PRAISE Trial)

RESEARCH PROTOCOL
Version 1, 17th August 2023

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Authorised by:	Professor Matthew Wilson

Sheffield Clinical Trials Research Unit (CTRU)

Pain Relief After Instrumented Spinal surgEry trial

PRAISE trial

This document describes a clinical trial and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

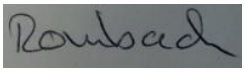
Authorisation Page

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, CTRU (and/or any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given. I also confirm that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Protocol authorised by:

Name, Role and Organisation	**Signature**	**Date**
Chief Investigator: Professor Matthew Wilson		23-Aug-23
Sponsor: Dipak Patel		23-Aug-23
Statistician: Dr Ines Rombach		23-Aug-23
Trial Manager: Marie Hyslop		23-Aug-23

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Abbreviations

Definition of terms

AE	Adverse Event
CCC	Confirmation of Capacity and Capability
AR	Adverse Reaction
ASA	American Society of Anaesthesiologists
CA	Competent Authority
CEAC	Cost-Effectiveness Acceptability Curves
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DPA	Data Protection Act
DSUR	Development Safety Update Report
EC	European Commission
EEACT	Economic Evaluation Alongside a Clinical Trial
ESPB	Erector Spinae Plane Block
EMEA	European Medicines Agency
EQ-5D-5L	Quality of Life Questionnaire
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GAD-7	Generalised Anxiety Disorder Assessment
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HTA	Health Technology Assessment
IB	Investigator Brochure
ICC	Intraclass Correlation Coefficient
ICF	Informed Consent Form

ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
ITO	Intrathecal Opioid
IV	Intravenous
LOS	Length of Stay
Kg	Kilograms
MA	Marketing Authorisation
Mg	Milligrams
Ml	Millilitre
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIHR	National Institute of Health Research
NIMP	Non-Investigational Medicinal Product
NMB	Net Monetary Benefits
NSAID	Non Steroidal Anti Inflammatory Drug
ODI	Oswestry Disability Index
PHBQ-9	Patient Health Questionnaire
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PONV	Post-Operative Nausea & Vomiting
PSF	Pharmacy Site File
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
QoR-15	Quality of Recovery Scale
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UC	Usual Care
VAS	Visual Analogue Scale
TSC	Trial Steering Committee

1. General information

1.1 Investigator details

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1.6 Funder

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1.7 Protocol Amendments

No protocol amendments in this current version.

Trial Summary

Study title	Pain Relief After Instrumented Spinal surgEry trial (PRAISE Trial)
Sponsor	Sheffield Teaching Hospitals NHS Foundation Trust
Funder	NIHR HTA (NIHR153170)
ISRCTN	TBC
Project start date	1st September 2023
Project end date	31st August 2026
Hypothesis	Enhanced analgesic techniques, intrathecal opioids or Erector Spinae plane Block, improve postoperative back pain on moving around the bed (sitting up and/or turning) at 24 hours by at least 10 points (0-100 Visual Analogue Scale) compared to usual care in patients undergoing spinal surgery +/- decompression.
Aims	To investigate the clinical and cost effectiveness of three approaches to postoperative pain relief following lumbar spine surgery.
Objectives	An RCT powered to test the hypothesis that enhanced anaesthetic techniques, intrathecal opioids or Erector Spinae plane Block, improve postoperative back pain on moving around the bed (sitting up and/or turning) at 24 hours by at least 10 points (0-100 Visual Analogue Scale) compared to usual care (multimodal pain relief including intravenous opioid, paracetamol, local infiltration of surgical incision with Local Anaesthetic) in patients undergoing spinal surgery +/- decompression.

	An economic evaluation alongside a clinical trial (EEACT), from an NHS and societal perspective.
Study design	A multicentre, parallel group, superiority, patient-blinded, individual participant-randomised controlled trial with 1:1:1 allocation to usual care (UC), usual care plus intrathecal opioid (ITO) and usual care plus Erector Spinae Block (ESB). Including an internal pilot phase and economic evaluation.
Internal pilot/feasibility criteria	Internal red, amber or green stop/go pilot feasibility criteria, to determine the feasibility of a full-scale trial (20 months from start of grant) in terms of: 1. Recruitment 2. Intervention Delivery (number of patients receiving randomised treatment) 3. Site Setup 4. Availability of pain score (primary outcome)
Setting	UK NHS Hospitals carrying out posterior lumbar instrumented spinal surgery +/- decompression.
Participants	People aged 16 and over, scheduled for elective, posterior lumbar-instrumented spinal surgery +/- decompression, who are able to give informed consent.
Inclusion Criteria:	• People aged 16 or over. • Scheduled for elective, posterior lumbar-instrumented spinal surgery +/- decompression.

	• Able to give informed consent, with interpreters provided where necessary.
Exclusion Criteria	• Patients with drug sensitivity or allergy to any of the trial agents i.e. intrathecal opioid or local anaesthetic • Patients undergoing fusion at more than three vertebral levels • Patients with an infection or tumour at the block site or surgical site • Patients meeting the criteria for American Society of Anaesthesiologists Grade 4-5 • Patients undergoing surgery during an emergency admission. • Patients scheduled for single-level microdiscectomy and decompression. • Current pregnancy: a pregnancy test, in the female patients of childbearing age is routine immediately prior to surgery. In the event of a positive test, surgery would be deferred until after the pregnancy was complete.
Intervention and control groups	**Control: Usual care (UC)** - multimodal pain relief: intravenous opioid, paracetamol, NSAID (if not contraindicated), local infiltration of surgical incision with Local Anaesthetic, is currently usual care in the UK, with variation between centres.

	Intervention 1 (ITO) - Usual Care plus Intrathecal Opioid injection under direct vision at the time of surgery. Local infiltration of surgical incision with Local Anaesthetic. **Intervention 2 (ESB)** – Usual Care plus Erector Spinae plane Block, a regional field block with local anaesthetic. No local wound infiltration.
Primary outcome(s)	Primary outcome is back pain on moving around bed (sitting up and/or turning) on a 0-100 VAS at 24 hours post-surgery
Secondary outcome(s)	Secondary outcomes include EQ-5D-5L, back pain at rest, leg pain, QoR-15, cumulative postoperative opioid consumption, quality of life, time to mobilisation, length of stay, adverse events, side-effects and healthcare resource use. Parallel economic evaluation with the trial will estimate incremental cost-effectiveness ratios
Duration of recruitment period and first enrolment date	15 months (first enrolment planned September 2024)
Duration of follow-up	Participants will be followed up 6-8 weeks after their surgery.
Target sample size	456 participants (152 per group)
Definition of end of trial	The end of the trial is defined as the date of the last recruited participant's post-surgery follow up visit. Sites will be closed once data cleaning is completed and the regulatory authority and ethics committee will be informed.

2. Introduction

2.1 Background

Spinal surgery is common; in 2019/20 there were over 55,000 operations, of which HES data recorded 2,635 (5%) posterior instrumented lumbar spine fusions, 1,659 (63%) were in working age people. Pain after instrumented lumbar spinal surgery is severe and can persist for many weeks, with a mean length of hospital stay of 4.7 days. Severe postoperative pain can delay early mobilisation, with potential complications such as venous thromboembolism and infection, all of which carry costs for the NHS, including an estimated £350 a day for an orthopaedic inpatient stay. Standard pain relief in the UK incorporates multimodal analgesia, including strong opioids, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs); this is widely available, cheap and relatively effective for many people.

Alternative techniques may improve current care. Intrathecal opioid injection, under direct vision, into the cerebrospinal fluid, at the time of surgery, by a surgeon is conventional in some NHS centres. Central (neuraxial) opioids provide effective pain relief for many hours after surgery by blocking spinal opioid receptors in the *Substantia Gelatinosa*, reducing the onward transmission of nociceptive stimuli from the Central Nervous System. Intrathecal opioids have been shown to reduce the requirement for systemic (intravenous) opioids and improve reported pain scores. Potential side effects include respiratory depression, pruritus, post-operative nausea & vomiting (PONV) and urinary retention[1,2]. There is currently no clinical consensus about whether intrathecal opioids should be used routinely. Systematic reviews of low-moderate quality studies show reduced pain scores and analgesic consumption, no effect on length of stay, PONV, sedation, respiratory depression, headache or urinary retention and an increase in pruritus[1,2]. The advantage of intrathecal morphine was only as large as including NSAIDs in post-operative multimodal analgesia[3]. It is important to acknowledge that intrathecal administration of morphine or diamorphine is technically a practice not covered by the specifics of product licensure. However, their use in perioperative analgesia has been widespread for more than two decades and represents a care standard which is internationally recognised. Their use is not confined to spinal surgery and they are prescribed ubiquitously for other common surgical interventions, including Caesarean Section and Total Joint replacement (Hip and Knee). The wealth of trial evidence and systematic reviews of ITO administration for spinal surgery included in the literature review for this study attests to their widespread, international clinical use and the "Commission" to conduct this trial could not have failed to recognise this when an evaluation of their effectiveness was requested. Centres

participating in the trial will each have well developed and long standing local Trust based guidance for the administration of intrathecal opioids which trial procedures will adhere to. This local guidance for the care standard will be supplemented by product information provided to the bodies governing their use in the context of a clinical trial. For many participating centres, there will be well developed practices already in place to facilitate ITO administration when it is dictated by randomised group allocation. For these reasons and the overwhelming weight of experience from current clinical practice, the investigators are confident to assert that it is appropriate to use a SmPC for intrathecal opioids despite them being administered by a route not technically adherent to the product license. Section 4.8 of the morphine and diamorphine SmPCs will be used as the Reference Safety Information to complete the required safety and expectedness assessments for the trial.

Recently, "Fascial" plane peripheral nerve blockade, with local anaesthetic, has been proposed for the provision of pain relief after spinal surgery, specifically Erector Spinae plane Block (ESB). The mechanism of analgesia is the interruption of pain sensory input from the area of surgery arising via the dorsal rami of spinal nerves, with the potential advantage of reducing the doses of post-operative opioid required[4–6]. The skill set to perform ESB under ultrasound guidance requires training and practice to achieve competence and is not ubiquitous among all anaesthetic practitioners, limiting its generalisability in the NHS. Block failure, infection, pneumothorax (if ESB performed at thoracic levels) and inadvertent intravenous injection are potential adverse events. Systematic reviews reported that ESB reduces 24 hour postoperative opioid requirements, pain scores up to 24 hours, the risk of PONV and LOS, with increased patient satisfaction compared to standard care[7,8]. Heterogeneity and risk of bias resulted in appeals for large, high quality RCTs to evaluate ESB.

Standard care is subject to competing and heterogeneous guidance. Intrathecal opioids can involve different drugs e.g. morphine or diamorphine, again with no overarching guidance to direct their administration or standards for aftercare, which are left to individual units to interpret. Different drug profiles can have implications for the level of aftercare required; intrathecal morphine may necessitate postoperative High Dependency Care with additional resource implications. Widespread adoption of ESB would require substantial resources and investment to train an entire cadre of anaesthetists to make it routinely available to patients. Intrathecal morphine and ESB have been compared in small hepatectomy[9] and Caesarean Section[10] studies, but not in spinal surgery. The relative benefits of either intervention may

not justify the increase in procedural complexity and side effects, warranting our usual care arm.

2.2 Rationale for current study

Spinal surgery is common in the NHS and can result in severe postoperative pain limiting recovery and rehabilitation. The treatments under evaluation each carry a different harm:benefit profile. Multimodal analgesia with strong opioids (Usual Care) is standard treatment but there is some evidence from systematic reviews that the alternatives may offer superior pain relief. Both intrathecal opioids and ESB are currently used in some centres, but without a rational basis for treatment selection in scientific evidence. In some centres postoperative High Dependency Unit admission is mandatory for respiratory monitoring of patients receiving ITO. Evaluation against ESB is necessary since, if proven to be superior, its adoption would require a national programme to train anaesthetists in ultrasound-guided regional Anaesthesia. ESB carries a risk of rare, but serious complications unique to regional anaesthesia techniques. Evidence from a recent trial suggests that ESB confers no advantage in postoperative opioid consumption, bringing its value into question[11]. ESB will be compared to Usual Care and ITO will also be compared to Usual Care. The latter two techniques will use Levo-bupivacaine for local (skin) wound infiltration, at the end of the procedure, in a dose comparable to that administered in the ESB arm. This will provide a valid test of ESB effectiveness relative to local anaesthetic delivered by another means. Levobupivacaine has been selected as the local anaesthetic of choice since it is widely available, in common use within clinical practice and possesses the best safety profile for regional analgesia. The product characteristics for Levo-bupivacaine stipulate that a 2.5% concentration solution should be utilised for local infiltration, however the use of 0.5% concentration Levo-bupivacaine, to deliver the same total dose of local anaesthetic, with a smaller total volume of solution, is also in widespread use in peri-operative practice despite this technically being classed as “off label.” The maximum dose of Levo-bupivacaine administered will not exceed 2mg/kg however the drug is delivered. Despite the drug being used routinely in standard of care, Section 4.8 of the levobupivacaine SmPC will be used as the Reference Safety Information to complete the required safety and expectedness assessments for the trial.

Economic evaluation is essential to evidence the value of new care standards to patients and the NHS relative to usual care which is cheap, widely available and effective for the majority of recipients.

The study will be conducted in accordance with the protocol, GCP and the Medicines for Human Use (Clinical Trials) Regulations 2004.

3. Aims and objectives

3.1 Aims

The main aim of this trial is to investigate the clinical and cost effectiveness of two novel approaches to postoperative pain relief following lumbar spine surgery (ITO including local infiltration and ESB) against the current standard of care.

3.2 Objectives

3.2.1 Main Objective:

- An RCT powered to test the hypothesis that enhanced anaesthetic techniques, intrathecal opioids or Erector Spinae plane Block, improve postoperative back pain on moving around the bed (sitting up and/or turning) at 24 hours by at least 10 points (0-100 Visual Analogue Scale) compared to usual care in patients undergoing spinal surgery +/- decompression.

3.2.2 Clinical Objectives:

- To determine if there is a difference in cumulative opioid consumption after surgery, at 24 hours and 72 hours (or discharge) (converted to oral morphine equivalent), between UC, ITO and ESB;
- To determine if there is a difference in quality of recovery between the three intervention groups using the Quality of Recovery Scale
- To compare the adverse events between UC, ITO and ESB;
- To compare the intervention-related side-effects (including: Postoperative Nausea and Vomiting (PONV), pruritus, respiratory depression (respiratory rate <8 breaths/minute) between UC, ITO and ESB;
- To determine if there is a difference in the need for further clinical intervention such as: antiemetic administration, urinary catheterisation, High Dependency Care/Intensive Care admission, between UC, ITO and ESB;
- To determine if there is a difference in time to mobilisation after surgery and length of hospital stay (readiness for discharge) between UC, ITO and ESB;
- To determine if there is a difference in readmissions between discharge and routine 6-8 week postoperative follow up, between UC, ITO and ESB.

- To determine if there is a difference in quality of life between the three intervention groups
- To determine if there is a difference in healthcare resource use between the three intervention groups.

3.2.3 Feasibility Objectives:

To undertake an internal pilot trial to determine the feasibility of a full-scale trial, in terms of:

- Recruitment
- Intervention Delivery (number of patients receiving randomised treatment)
- Site Setup
- Availability of pain score (primary outcome) data

3.2.4 Health Economic Objectives:

- An economic evaluation alongside a clinical trial (EEACT) from an NHS and societal perspective.

4. Trial Design

This is a multicentre, parallel group, superiority, patient-blind, individual participant-randomised controlled trial to evaluate enhanced anaesthetic techniques, intrathecal opioids or Erector Spinae Plane Block (ESB), in improving postoperative back pain on moving around the bed (sitting up and/or turning) at 24 hours compared to usual care in patients undergoing spinal surgery +/- decompression. The study will be conducted in around twenty-five NHS trusts and will involve an internal pilot to evaluate recruitment, site setup, pain scores and intervention delivery.

Participants will be randomised with 1:1:1 allocation to one of the three groups:

- Usual care (UC),
- Usual care plus intrathecal opioid (ITO)
- Usual care plus Erector Spinae Block (ESB).

Usual Care: Multimodal pain relief using a combination of simple and strong systemic opioid analgesia is currently standard care after spinal surgery +/- decompression. Analgesia is administered at the time of surgery whilst under General Anaesthesia. Intravenous opioid,

Paracetamol, NSAID (if not contraindicated) administered intra-operatively at discretion of local anaesthetist. Local Wound Infiltration of surgical incision with Local Anaesthetic (levo-bupivacaine) at surgical closure by operating surgeon.

Intrathecal Opioid (ITO): Pain relief with Central (neuraxial) opioid pain relief, reducing onward transmission of nociceptive stimulus to reduce patient pain sensation for sustained period post operatively. Intrathecal Opioid Analgesia, Morphine or Diamorphine, administered by operating surgeon during surgery. ITO group will receive intervention plus Usual Care. Wound Infiltration of surgical incision with Local Anaesthetic (levo-bupivacaine) at surgical closure by operating surgeon.

Erector Spinae Plane Block (ESB): To interrupt pain signal transmission from the area of surgery to the Central Nervous System with local anaesthetic nerve blockade. Ultrasound-guided injection of local anaesthetic levo-bupivacaine, to produce a bilateral "Fascial Plane" block, administered by ESB-trained anaesthetist at time of surgery, prior to emergence from anaesthesia. Erector Spinae Block group will receive the intervention plus Usual Care, without Local Wound Infiltration.

In the event of pain relief being inadequate, or wearing off in the period of assessments in any of the 3 trial arms, rescue analgesia will be provided by systemic opioid pain relief, administered according to local practice and guidance.

4.1 Blinding

Participants will be blinded to allocation. Surgeons, anaesthetists and treating clinicians will be aware of allocation at the time of surgery. The patient-reported primary outcome will be collected by a blinded observer; key secondary outcomes are objective and robust to knowledge of group allocation. Clinical staff administering postoperative analgesia will be blinded to allocation as far as practical, making clinical judgements in accordance with routine pain assessments.

Any instances of suspected unblinding, either in patients or blinded outcome assessors, will be recorded, including the reasons for and time point of unblinding. Participants will also be asked at the end of their participation if they are aware, or think they are aware of their allocated treatment group. Any episodes of formal unblinding, at the request of clinical care

teams, to inform therapeutic decisions will be recorded, with details of the reasons for request. The overall rate of unblinding and preservation of data integrity shall allow the trial steering committee to make an informed decision on trial feasibility and also allow discussion of future steps to improve blinding where necessary.

4.2 Feasibility Pilot

There will be an initial phase of the trial that will be an internal pilot. The proposed length of the internal pilot phase is 20 months (8 months into recruitment). Sheffield CTRU will aggregate study data to assess the feasibility of the research and intervention protocols based on the following feasibility outcomes:

Table 1. Proposed 20 month internal pilot

Criterion	Red (% complete)	Amber (% complete)	Green (% complete)
Site set up (number of centres set up and recruited their first participant)	<10 centres (<50%)	10-19 (50-94%)	20 (100%)
Participant recruitment (percentage of overall target recruitment rate as per Gantt chart)	<60% (<126 participants)	60-99% (126-209 participants)	100% (210 participants)
Availability of pain score (primary outcome) Numerator = number with 24hr pain score recorded Denominator = Number randomised, excluding those randomised who have not had surgery yet but including those randomised who have withdrawn or did not have the intervention as randomised).	<70% (<147 participants)	70-99% (147-209 participants)	100% (210 participants)
Intervention delivery (number of patients receiving randomised treatment) Numerator = number receiving the randomised treatment Denominator = number randomised, excluding those randomised who have not had surgery yet but including those randomised who have withdrawn or did not have the intervention as randomised	<75% (<158 participants)	75-99% (158-209 participants)	100% (210 participants)

It is noted that there is likely to be a delay between randomisation and procedure, due to surgery waiting times and the need to randomise early enough to ensure availability of components of intervention delivery on the day of surgery.

At the pilot assessment point, if all criteria are reported at the green threshold, the trial will be recommended to continue without changes. If all criteria are at amber or above, the proposal will be to continue the trial, with a specific plan to address those criteria in amber. If any of the criteria are reported in the red boundary, this will be discussed with the TSC, DMEC, and the NIHR as to whether it is feasible to continue the trial as planned. Depending on the reasons for criteria not meeting amber or above, mitigations may be put in place to address the issue. The funder will be at the forefront of decision-making at the end of the pilot phase, and the TSC and DMEC will be consulted ahead of reporting at the end of the pilot phase, regardless of actual performance.

5. Selection of participants

We aim to recruit 456 adults over 16 years old who are scheduled for elective, posterior lumbar-instrumented spinal surgery +/- decompression. The trial will be run nationally within the UK across up to twenty-five centres. Participating hospitals will represent multi-ethnic, deprived and underserved areas, in large teaching hospitals and smaller district generals where this surgery is performed.

5.1 Inclusion criteria

- People aged 16 or over.
- Scheduled for elective, posterior lumbar-instrumented spinal surgery +/- decompression.
- Able to give informed consent, with interpreters provided where necessary.

5.2 Exclusion criteria

- Patients with drug sensitivity or allergy to any of the trial agents i.e. intrathecal opioid or local anaesthetic
- Patients undergoing fusion at more than three vertebral levels
- Patients with an infection or tumour at the block site or surgical site
- Patients meeting criteria for American Society of Anaesthesiologists Physical Status Classification Grade 4-5[12]

- Patients undergoing surgery during an emergency admission (this would preclude a detailed risk-benefit conversation with a consultant anaesthetist, which our PPI group told us was vital pre-consent).
- Patients scheduled for single-level microdiscectomy and decompression.
- Current pregnancy: a pregnancy test, in the female patients of childbearing age is routine immediately prior to surgery. In the event of a positive test, surgery would be deferred until after the pregnancy was complete.

5.3 Participant identification

Patients listed for posterior lumbar-instrumented spinal surgery +/- decompression will be recruited from adult spinal clinics. Potential study participants will be identified by spinal surgeons when a decision to proceed with surgery is taken. Data will be collected from all participants on geographical location (first part of postcode), age, sex and ethnicity, work, and if there are concerns during the trial that certain groups are not adequately represented, advice will be sought on how to maximise opportunities for these groups. This will ensure that the research sample represents the target population.

5.4 Informed consent process

New patients will be identified and screened for eligibility by the surgical clinical team when the decision for lumbar spinal surgery has been taken. Patients will be provided with written information materials and referred to an anaesthetist for an in-depth trial discussion. There will be a clear explanation of study procedures including the interventions and associated risks, and the opportunity for patients to have any questions. Written information sheets will be thorough and will include clear information on how study interventions differ from those patients may have received in the past, such as spinal anaesthesia or epidurals.

Consent will only be sought after the discussion with the anaesthetist has taken place. Eligibility and consent can only be taken by a medically-qualified individual on the delegation log. Recruitment will be aligned around the standard care pre-operative assessment appointment. This will take place sometime after the patient has initially been listed for surgery, and therefore provides the ideal point for randomisation to occur, allowing sufficient time for the patients to consider the information and decide whether they would like to take part. Consent and acquisition of baseline questionnaire information can occur at pre-operative assessment clinic or at another point prior to surgery, depending on the local model of pre-operative care. Consent can be taken remotely in accordance with the procedures

detailed in the relevant study specific manual/SOP where permitted locally. Randomisation will occur once consent is confirmed (see section 7). This also allows sufficient time after randomisation to ensure appropriately trained staff and Investigational Medicinal Products (IMPs) are available on the date of surgery for the allocated intervention.

As study outcome collection is aligned with standard care appointments, or during a hospital stay, participant expenses will not be covered by the trial.

5.5 Co-enrolment guidelines

Concurrent participation in any other interventional clinical study should be discussed with the central trial team prior to participant enrolment in PRAISE.

5.6 Pregnancy

Females of childbearing age potential will receive a pregnancy test as routine on the day of surgery, prior to the surgery and IMP administration taking place. If positive, surgery would not proceed due to risks associated with general anaesthesia and ionising radiation, and the patient would be withdrawn from the trial. Emergency surgery is excluded from this trial.

As the effects of the IMP and anaesthetic technique are short-lived, there will be no follow up of any pregnancy that occurs after a participant has received the intervention.

6. Trial treatment

6.1 IMP details

In this trial, the IMPs include: morphine, diamorphine and levo-bupivacaine and are detailed for each intervention below. All IMPs will be sourced from local hospital stock within the participating centres. No segregation of trial supplies is required and no trial specific storage arrangements or temperature monitoring arrangements are required. Morphine and Diamorphine must be dispensed from research pharmacy in vials for use within the trial in theatre on a per-patient basis. Site pharmacies will apply a clinical trial label complying with the requirements set out in the IMP manual at the point of dispensing. Sites must not use theatre-stock pre-filled syringes of morphine or diamorphine under any circumstance for the trial. Levo-bupivacaine can be sourced from local theatre stock as per local standard practice. There will be no labelling requirements for levo-bupivacaine. A separate IMP manual details IMP handling, labelling and recording requirements, particularly for morphine and

diamorphine use. Accountability for all drugs must be kept as per the IMP manual and Data Collection manual. Participants will be randomised 1:1:1 to receive one of the three interventions.

6.2 Patients randomised to Intervention 1: Usual Care

Involves analgesia administered at the time of surgery whilst under General Anaesthesia and in the immediate post-operative period. Intravenous opioid, Paracetamol, NSAID (if not contraindicated). This will be administered by the anaesthetist providing clinical care. Trial participants will also receive local infiltration of surgical incision with Local Anaesthetic (Levo-Bupivacaine) administered by the Operating Surgeon

How: Intravenous injection during surgery in Operating Theatre. Local anaesthesia administered at surgical closure.

Timing: Intravenous drugs administered intra-operatively. Local anaesthetic infiltration at completion of surgery.

Dose: Intravenous analgesia administered at the discretion of the Consultant anaesthetist: Local Anaesthetic Infiltration: up to maximum dose Levo-Bupivacaine 100mg

Tailoring: Opioid Analgesia Drug Type and Dose administered according to Anaesthetist's clinical opinion and local practice. Paracetamol as per local standard of care, NSAID if not contraindicated.

Modifications: Local anaesthetic infiltration volume adjusted to maximum dose of Levo-Bupivacaine 2 mg/kg to avoid toxicity.

Accountability: All drugs administered during surgery are routinely recorded in anaesthetic record.

6.3 Patients randomised to Intervention 2: Intrathecal Opioid (ITO)

Involves pain relief with central (neuraxial) opioid pain relief, reducing onward transmission of nociceptive stimulus to reduce patient pain sensation for sustained period post operatively. Intrathecal Opioid Analgesia administered by operating surgeon at the time of surgery whilst under General Anaesthesia. Morphine (Preservative Free); diamorphine according to local clinical practice guidelines. ITO plus Usual Care as above.

How: Intrathecal Opioid administered by Operating Surgeon in Operating Theatre. Intrathecal injection under direct vision, via narrow gauge "pencil point" spinal needle via Ligamentum Flavum. ITO is permitted to be administered by an appropriately trained surgeon who does

this procedure as part of their clinical care. The usual care and intrathecal opioid interventions are routinely used in the NHS and require no specific training.

Timing: At the time of surgery. Local wound infiltration at completion of surgery.

Dose: Preservative Free Morphine: 0.1 mg (minimum dose); or Diamorphine (dose range 0.2mg to 0.4mg).

Modifications: Choice of drug (morphine vs diamorphine) dictated by local practice and requirements for post-operative care. Paracetamol as per local standard of care. Omit NSAID if contraindication.

Accountability: Morphine or Diamorphine must be dispensed from research pharmacy. Confirmation of intrathecal administration by cerebrospinal fluid aspiration prior to injection. All drugs administered during surgery are routinely recorded in anaesthetic records, which will inform the per protocol analysis.

Intrathecal Opioid Group will receive Usual Care, as described in 6.2, plus the Intervention described above.

6.4 Patients randomised to Intervention 3: Erector Spinae Block

Interrupts pain signal transmission from the area of surgery to the Central Nervous System with local anaesthetic nerve blockade. Regional "Field" Block with local anaesthetic, given by Anaesthetist having completed the Trial ESPB training.

How: Ultrasound-guided injection of local anaesthetic, to produce a bilateral "Fascial Plane" block. Given in Operating Theatre at time of surgery, prior to emergence from anaesthesia.

Dose: 2 x 20 mls Levo-Bupivacaine 0.25% (2.5 mg/ml), 40 mls in total. 0.25% Levo-Bupivacaine is widely available "off the shelf" in all operating theatres. Using a standard solution, without the need for mixing drugs prior to administration, minimises the potential for drug error. The volume and dose chosen will be effective in the majority of patients who will be substantially heavier than 50kg. Adjusting the volume down, rather than altering concentration, in the small number of patients below 50kg, likewise reduces the chance of drug error or local anaesthetic toxicity. The concentration and volume of Levo-Bupivacaine for local infiltration in Usual Care was chosen to emulate routine clinical practice and deliver the same dose of drug as local infiltration (20 ml 0.5% = 100 mg).

Modifications: If patient weight < 50kg: Reduced Volume of Levo-Bupivacaine to maximum dose 2 mg/kg (e.g. 45 kg patient would receive 90 mg Levo-Bupivacaine or 36 mls as 2 x 18 mls injections) to avoid the potential for local anaesthetic toxicity. Paracetamol as per local standard of care: Omit NSAID if contraindication.

Accountability: Drug delivered to correct "Plane" by direct, real time ultrasound visualisation. Confirmation of drug delivery by ultrasound "screen capture" after bilateral injection.

Erector Spinae Block group will receive Intervention described above *plus* Usual care, *without* Local Wound Infiltration.

6.5 Training for Erector Spinae plane Block

The Erector Spinae plane Block (ESB) arm requires training for participating anaesthetists who do not currently perform this procedure. This training process has been designed and will be administered by co-applicant McLeod who is internationally recognised for assessment of expertise in regional anaesthesia skills. Full details of the training package and evidence of training for anaesthetists taking part in the trial are documented within the Trial Master File.

6.6 Dose Modification and interruptions

Dose modifications according to patients' weight are noted above. The maximum dose of Levo-bupivacaine, should not exceed 2mg/kg in any circumstances.

6.7 Overdose

Overdose is very unlikely in this trial, and the only circumstances in which this may occur would be due to a drug calculation error. Local anaesthetic toxicity is possible, with the correct dose but this rare complication is described in the participant information materials and if they were to occur, would be treated according to nationally recognised guidelines.

7. Randomisation and enrolment

Once eligibility has been confirmed and consent acquired, the participant will be randomly allocated to one of the following groups: (1) Usual Care; (2) Intrathecal Opioids (ITO); (3) Erector Spinae plane Block (ESB) using the Sheffield CTRU online randomisation system (SCRAM). The doctor or research nurse will access the web-based randomisation system, patient demographic details (ID, date of birth) will be entered and the treatment allocation will be returned. Participants will be allocated to their intervention using minimisation with a random element and the following factors ensuring baseline balance: site; levels of fusion (1 level vs. >1 level (2-3)), receiving Step 3 opioid therapy at randomisation (yes vs no). Trial participants can only be randomised if staff trained in delivery of all interventions are available. Randomisation will be as close to the date of surgery as possible to allow the site to

ensure availability of the resources required to deliver either of the intervention arms and ensuring protocol adherence. Due to current NHS surgical waiting times, it is possible that patients could wait longer than 6 weeks after randomisation before their surgery takes place. If surgery is delayed beyond 6 weeks after randomisation, eligibility will be reconfirmed in advance of, or on the day of surgery taking place.

The delay between randomisation and treatment inevitably will lead to some post-randomisation, pre-intervention withdrawals, but the number is expected to be low for this type of elective surgery: Small numbers may not receive their randomised intervention due to staff availability or rescheduled surgeries, and these will be analysed as randomised. Participants will be blind to allocation and the success of their blinding will be assessed during their follow up.

8. Outcomes

8.1 Primary outcome

Back pain on moving around the bed (sitting up and/or turning) from Visual Analog Scale (VAS) recorded at 24 hours after surgery, reported using a 10 cm line, 0-100 score. Patients unable to sit up and/or turn as a result of pain will be assigned the highest pain score (100).

8.2 Secondary outcomes

Patient-reported outcomes

1. Pain scores (VAS) [13] back & leg pain, at rest and movement, on a 0-100 scale;
2. EQ-5D-5L[14]: Health status questionnaire used to derive quality adjusted life year (QALYs) and used in the cost-effectiveness analysis;
3. Quality of Recovery Questionnaire (QoR-15) [15] to measure the quality of recovery after surgery and analgesia;
4. Healthcare Resource Use: measured using a bespoke questionnaire.
5. Oswestry Disability Index[16] to measure functional recovery after surgery

Clinical

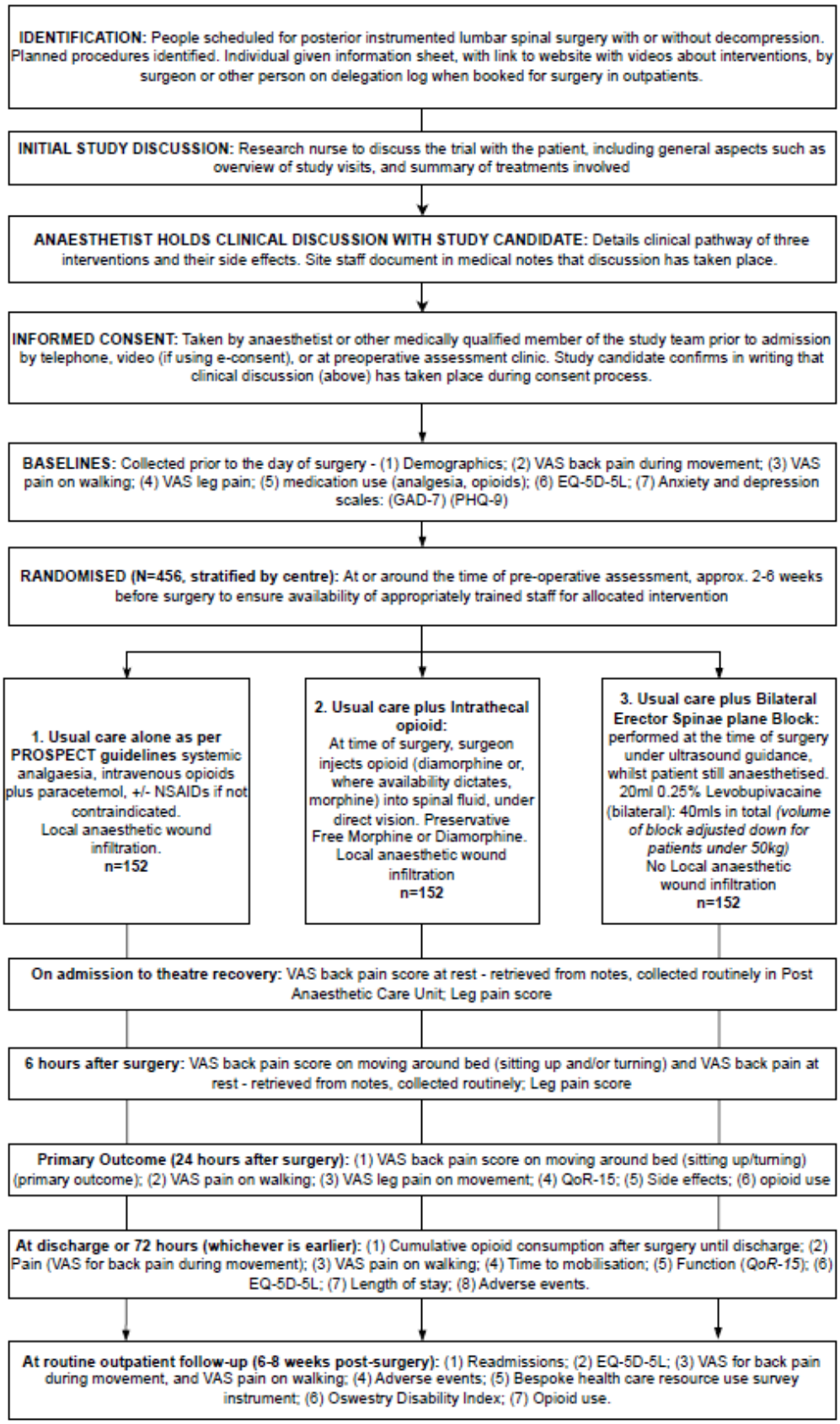
1. Cumulative opioid consumption after surgery, at 24 hours and 72 hours (or discharge) (converted to oral morphine equivalent)
2. Adverse events

3. Intervention-related side-effects (including: Postoperative Nausea and Vomiting (PONV), pruritus, respiratory depression (respiratory rate <8 breaths/minute)
4. Further clinical intervention such as: antiemetic administration, urinary catheterisation, High Dependency Care/Intensive Care admission
5. Time to mobilisation after surgery
6. Length of hospital stay (readiness for discharge)
7. Readmissions between discharge and routine 6-8 week postoperative follow up.

The timing of all outcome assessments is shown in Table 2.

9. Assessments and procedures

9.1 Trial Flow Chart



9.2 Study Assessment Schedule

Table 2. Assessments during trial

The following data collection windows will be permitted for the collection of follow up data:

- 6 hours after surgery +/- 2 hours
- 24 hours after surgery +/- 12 hours
- At discharge or 72 hours after surgery – if 72 hours is used (+/- 12 hours)
- 6-8 weeks after surgery

	Baseline		**On admission to theatre recovery**	**6 hours after surgery**	**24 hours after surgery**	**At discharge or 72 hours (whichever is earlier)**	**6-8 weeks after surgery (routine outpatient appointment)**
	Pre-randomisation	**Pre-operatively**					
Informed Consent	✓						
Eligibility	✓						
Randomisation	✓						
Demographics (age, sex, ethnicity, diagnosis)	✓						
Medication use (analgesia, opioids)	✓						✓
Cumulative opioid consumption					✓	✓	
Time to mobilisation						✓	
Length of stay						✓	
Patient reported measures							
VAS[13] back pain on moving around bed (sitting and/or turning)	✓			✓	✓ Primary	✓	
VAS back pain on walking	✓				✓	✓	✓

VAS back pain at rest			✓	✓			✓
VAS leg pain	✓		✓	✓	✓		✓
EQ-5D-5L[14]	✓					✓	✓
Anxiety and depression scales (GAD-7[17], PHQ-9[18])	✓						
Quality of recovery (QoR-15)[15]					✓	✓	
Healthcare resource use							✓
Oswestry Disability Index[16]							✓
Safety and complications							
Side effects and adverse events			✓	✓	✓	✓	✓
Readmissions							✓

Outcome data will be collected from health records by site research staff at baseline (pre-operatively), on admission to theatre recovery, at 6 and 24 hours after surgery, at discharge or 72 hours (whichever is earlier), and at 6-8 weeks post-surgery (routine outpatient visit) (Table 2). We will use routine outcome data wherever possible, to minimise costs and impact on both participants and clinicians. Patient demographics will be captured at baseline and assessed to evaluate equality, diversity and inclusion.

Baseline data will be collected by a research nurse or clinician (Table 2). Operative details will be recorded by the operating surgeon and anaesthetist. Twenty-four hour and six-eight week follow up data will be collected by a research team member who is blind to group allocation. Patient Reported Outcome measures (PROMs) data will be collected either on paper initially with subsequent data entry by site staff, or directly onto the study database via a tablet or computer. Pain scores (PROMs) in theatre recovery and 6 hours after surgery will be reported verbally by the patient and recorded by site staff.

9.4 Procedure for assessing safety

In addition to surgical complications attendant with spinal procedures, potential harms differ somewhat for each group allocation:

- Usual Care: inadequate analgesia (severe, acute postoperative pain) postoperative nausea and vomiting (PONV), sedation.
- Intrathecal Opioid: Respiratory depression, pruritus (itching), urinary retention.
- Erector Spinae Plane Block: very rare but potentially serious complications of delivery of local anaesthetic including intravenous injection, local anaesthetic toxicity, intraneural injection, infection at needle insertion site and pneumothorax.

Serious Adverse Events (SAEs) will be reported in accordance with the CTRUs standard operating procedure. All SAEs occurring from the point of informed consent up to the end of involvement in the trial (6-8 weeks post-surgery), will be reported immediately to the CTRU on recognition, apart from those identified as exempt. Delegated site trial staff will record all adverse events and make them known to the Principal Investigator and/or delegated sub-Investigator.

9.5 Participant withdrawals

Participants may withdraw their consent for the study at any time, without providing a reason for this. If this occurs, this will be documented on a study completion/ discontinuation form and the patient notes, and no further data will be collected for this participant for the study. Although the participant is not required to give a reason for discontinuing their study treatment, a reasonable effort will be made to establish this reason while fully respecting the participants' rights. Any data collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the patient at the time of consent. Participants will be asked at the point of withdrawal if they are happy for their routinely collected data to be used to inform trial outcomes.

Excessive participant withdrawal from follow-up has a negative impact on a study. Centres will explain the importance of remaining on study follow-up to participants, and that changes to planned treatment need not imply withdrawal from the study. Nevertheless, if participants do not wish to remain in the study their decision must be respected. If the participant explicitly states their wish not to contribute further data to the study, this will be recorded.

The delay between randomisation and treatment inevitably will lead to some post-randomisation, pre-intervention withdrawals, but these are expected to be low for this type of elective surgery: ~5% who become ineligible for surgery or withdraw for other reasons. The delay will be identical and withdrawals equally distributed across trial arms. In these cases, providing the patient agrees, they will be given the option to continue with follow-up despite withdrawing from the trial intervention.

9.6 Unscheduled visits

Participants local care team may also be part of the research team. Therefore, participants may be seen at additional visits outside those scheduled for the study, but these visits would be part of usual care. Any adverse events identified at additional usual care visits, will be documented in the CRF.

9.6 Loss to follow-up

Participants will be defined as lost to follow up if they do not attend their 6-8 week follow up visit. If a participant is lost to follow up, this will be recorded in the CRF using the study completion/discontinuation form. The risk of loss to follow up is low, as study visits align with standard care. All reasonable efforts will be made to contact patients for their appointments, including different methods of contact, or offers to collect partial follow up data by telephone if an in-person visit is not possible.

10. Safety Reporting

ICH-Good Clinical Practice (GCP) requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical studies. These procedures are described in this section.

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical study patient to whom a medicinal product has been administered irrespective of relationship
Adverse Reaction (AR)	Any AE that is judged, in the opinion of the PI, to be related to an investigational medicinal product or is the result of an

	interaction between an investigational medicinal product and a non-investigational medicinal product.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SmPC).
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Congenital anomaly/birth defect • Is otherwise considered medically significant by the investigator ***

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Recording and reporting

AEs and SAEs are defined as an event that occurs after the patient has provided written informed consent for trial entry and within 6-8 weeks of the last administration of trial treatment; i.e. until the end of the patient's participation in the trial. Any SAEs that are ongoing at this point, will be followed up to resolution.

All AEs and ARs will be recorded on the adverse event report form, within the participant CRF, including those that fulfil the criteria for being serious (see section 10.1). Sites are asked to enter all available information onto the study database as soon as possible after the site becomes aware of the event.

SAEs, SARs and SUSARs will require more detailed information to be recorded. In such cases, the event must also be reported to the Sheffield CTRU within 24 hours of the site becoming aware of the event.

In addition to surgical complications attendant with spinal procedures, potential harms differ somewhat for each group allocation:

- Usual Care: inadequate analgesia (severe, acute postoperative pain) postoperative nausea and vomiting (PONV), sedation.
- Intrathecal Opioid: Respiratory depression, pruritus (itching), urinary retention.
- Erector Spinae Plane Block: very rare but potentially serious complications of delivery of local anaesthetic including intravenous injection, local anaesthetic toxicity, intraneural injection, infection at needle insertion site and pneumothorax.

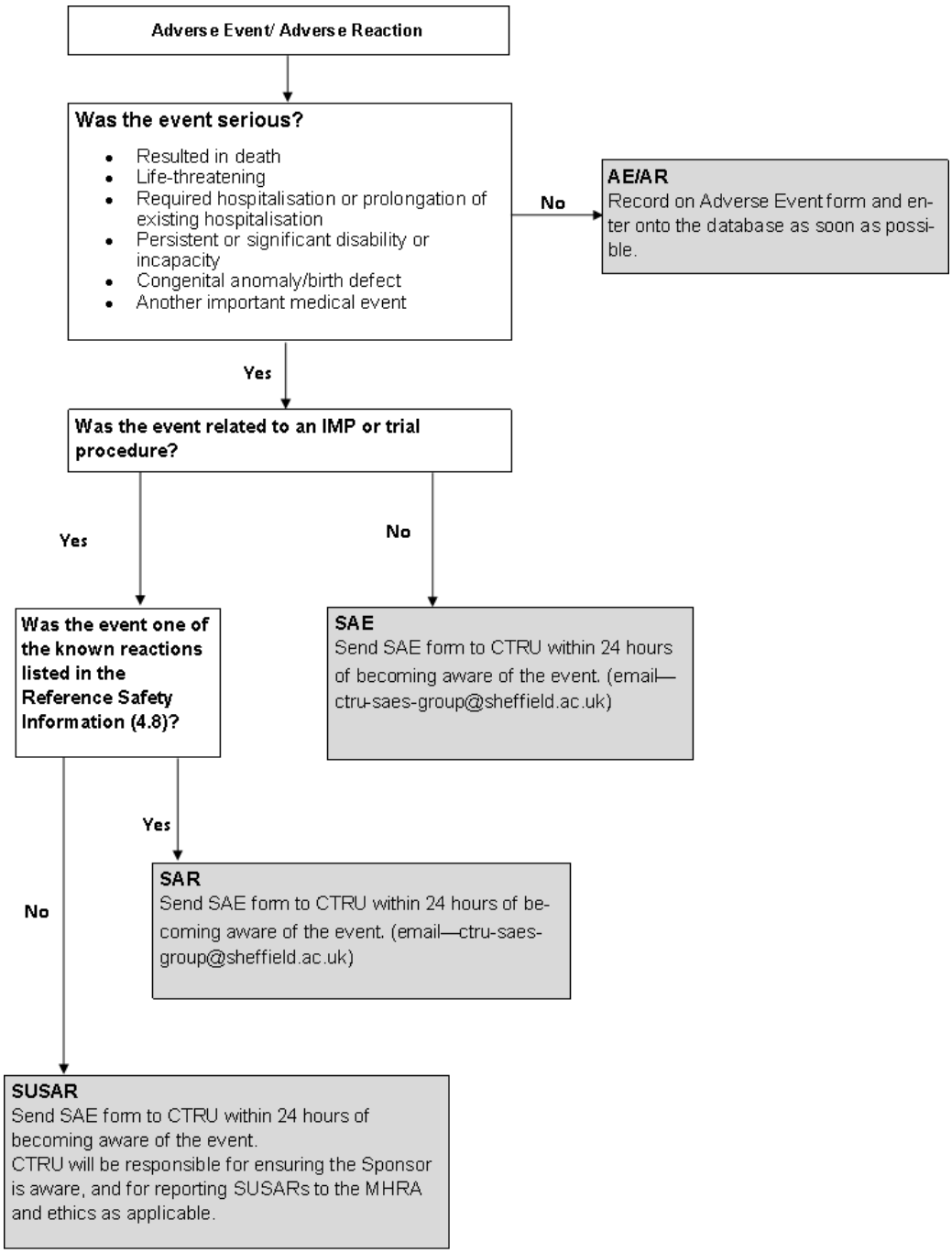
Serious Adverse Events (SAEs) will be reported in accordance with the CTRU's standard operating procedure. All SAEs occurring from the point of randomisation up to the end of involvement in the trial will be reported immediately to the CTRU on recognition. Delegated site trial staff will record all adverse events and make them known to the Principal Investigator and/or delegated sub-Investigator.

10.3 Study specific exemptions

Exemptions form the usual expedited reporting procedure:

- Intensive Care admission after surgery if this is planned as part of the procedure.
- Any wound infections that meet the criteria for an SAE need to be reported for the trial, but not specifically within the 24-hour reporting timeframe.

10.4 SAE notification procedure



10.6 CTRU responsibilities

An unexpected adverse reaction is an adverse reaction which is not previously reported in the Reference Safety Information (RSI) used in the study, or one that is more frequent or more severe than reported in the RSI. If a SAR is assessed as 'unexpected', it is classified as a SUSAR.

The RSI to be used in the study will be section 4.8 of the SmPCs in the version which has been submitted to and approved by the MHRA for this trial.

The Sponsor usually delegates CTRU responsibility for the reporting of SUSARs and other SARs to the regulatory authorities and the research ethics committee as appropriate. CTRU will also keep all investigators informed of any safety issues that arise during the course of the study.

10.7 SUSARs

If an SAE is identified as being a SUSAR and is fatal or life threatening, it will be reported by the Sheffield CTRU to the MHRA, the main REC, the Sponsor and all other interested parties within 7 days of being notified of the event. If an SAE is identified as a SUSAR and is not fatal or life threatening, it will be reported by Sheffield CTRU to the MHRA, the main REC, the Sponsor within 15 days of being notified of the event.

The DMEC and TSC will also receive information on all AEs and SAEs, at a frequency agreed with each committee and documented in the appropriate charter/terms of reference.

11. Statistics

11.1 Sample size

We will recruit 456 participants (152 per arm) to this trial. The primary outcome is a visual analogue scale (VAS) assessing patient reported back pain on moving around the bed (sitting up and/or turning) on a 0-100 scale. Our trial is powered to detect a clinically important difference of 10 points, using a standard deviation of 23[13], a two-sided 5% significance level, 90% confidence interval, and allowing for 10% loss to follow-up.

The sample size is further adjusted for clustering, as the intrathecal opioid will be delivered by surgeons, while anaesthetists will deliver the usual care analgesia, and specially trained anaesthetists or anaesthetic practitioners will deliver the ESB. We anticipate that, on average, 5 participants will be clustered within each interventionist. Intracluster correlations for early patient reported outcome measures were observed to be low[19], and we have adjusted for an ICC of 0.05.

The sample size is not adjusted for multiple testing, as a Hochberg multiple hypothesis testing procedure will be used to guide interpretation of results in order to claim statistical significance and superiority of the interventions. Specifically, ITO vs UC and ESB vs. UC will be tested first. No multiplicity adjusted is applied here, as these are comparisons of distinct

treatments versus a common control[20,21]. If both of these comparisons show a statistically significant difference, then we will perform the final statistical comparison of ITO vs. ESB, which can then be used to claim statistical significance and superior for this comparison.

The sample size is not adjusted for repeated measures of the primary outcome, as the primary follow-up time point is at 24 hours. No other follow-up time points will be included in the principal analysis of the primary endpoint as the study team were concerned about the potential for informative missing data at other time points.

11.2 Statistical Analysis

The primary outcome will be back pain on moving around the bed (sitting up and/or turning) measured on a 0–100 VAS at 24 hours post intervention. This analysis will include all participants with relevant outcome data based on their randomisation allocation. Differences in the primary endpoint will be estimated by a mixed-effects linear regression model, with fixed effects for randomisation factors (levels of fusion (1 level vs. >1 level (2-3)), step-3 opioid therapy at randomisation (yes vs. no)) and other important prognostic variables (including age, minimally invasive vs open fusion, decompression (yes vs.no), interbody fusion (yes vs. no)), and random effects for centre and person delivering the intervention. This model will only include the primary outcome at 24 hours, and no other primary outcome data collected at additional time points. This is due to concerns about the completeness of data at other time points, and potential bias that informative missingness may introduce into the statistical model.

As described above, for the primary endpoint, a Hochberg multiple hypothesis testing procedure will be used to guide interpretation of results in order to claim statistical significance and superiority of the interventions. Specifically, ITO vs UC and ESB vs. UC will be tested first. No multiplicity adjusted is applied here, as these are comparisons of distinct treatments versus a common control all three pairwise comparisons are of distinct treatments. If both of these comparisons show a statistically significant difference, then we will perform the final statistical comparison of ITO vs. ESB, which can then be used to claim statistical significance and superior for this comparison.

11.2.1 Supplemental analyses

The impact of missing primary outcome data will be minimised through careful data collection while participants are still in hospital. The primary analysis model assumes that data are missing at random, and will provide unbiased results if relevant predictors of missing data are included in the analysis model. As described previously, some participants may wish not to move due to pain, and hence will be unable to complete the primary endpoint. They will be assigned the worst possible pain score (100) for the purposes of the trial analysis.

The robustness of this analysis will be examined with sensitivity analyses under missing-not-at-random scenarios, whereby those with missing data are expected to have worse outcomes than those with available data[22]. We will investigate the effect of protocol non-adherence through analyses of the per-protocol population, excluding participants who do not receive their randomised treatment.

11.2.2 Secondary outcomes

Repeatedly measured continuous outcomes (pain scores, QoR-15, EQ-5D-5L, ODI) will be analysed using multilevel mixed-effects models including repeated measures for the outcome, nested within participants, and adjusted for randomisation and other important prognostic factors, including baseline outcome (fixed effects), randomising site and person delivering the intervention (random effect). Time will be treated as a categorical variable, and interactions between the treatment group and time will be included. Treatment effects with 95% confidence intervals will be presented for each follow-up time point. Continuous outcome measures that are only collected at one follow-up time point (e.g. time to mobilisation, length of stay) will be analysed in line with the primary analysis, or similar models. Treatment effects with 95% confidence intervals will be presented. Binary outcomes will be analysed using logistic regression models with similar adjustment for covariates.

11.2. Complications, Safety outcomes and adverse events

The following summaries will be presented: the number and percentages of patients reported as having SAEs in each treatment arm; the number and percentages recorded as having all forms of AEs in each arm; this will be presented as overall and stratified by AE classification. The number of participants requiring further interventions or revisions will be summarised descriptively.

12. Health Economics

An economic evaluation will be undertaken from the NHS perspective using the within-trial time frame (6-8 weeks). No modelling or estimation of cost-effectiveness over a lifetime horizon will be undertaken as the focus of the trial is on short-term pain immediately after surgery. Costs incurred for all participants will be obtained from hospital records up to the point of discharge. Cost of ITO and ESB will be obtained directly from the sites to estimate mean costs of each intervention. Cumulative opioid consumption and length of stay will be obtained from the hospital records at patient level. Additional resource use incurred between discharge and 6-8 week follow-up will be collected using a bespoke health resource use questionnaire, which will include additional medications, physiotherapy, potential use of other NHS services and return to work. Other related care contacts funded outside the NHS are not anticipated in the 6-8 week period.

Unit costs will be taken from standard sources: NHS Reference Costs/ Tariff, British National Formulary and 'Unit Costs of Health and Social Care'. The current NHS Reference Costs provide a cost per finished consultant episode, regardless of the actual length of stay. However, up to 2017/18 the average length of stay for each HRG and a cost per day for excess bed days were also available in relation to length of stay and cost per day. Therefore, to estimate accurate patient-level costs proportionate to the actual length of stay, the cost per day from the NHS Reference costs will be inflated to the current price using the NHS Cost Inflation Index.

EQ-5D-5L collected at baseline, discharge and 6-8 week follow up will be used to measure differences in health-related quality of life. Quality-adjusted life years (QALYs) gained will be estimated by calculating the area under the curve of linearly interpolated utilities between measurement points to cover the 6-8 week period. Within trial analysis will follow best practice guidelines[23]. The analysis will calculate total costs and QALYs for each patient and estimate the incremental costs and QALYs using a seemingly unrelated regression model with baseline covariates including age and baseline EQ-5D-5L score[24] to obtain cost-effectiveness and cost–utility estimates for each arm. Missing data will be imputed using multiple imputation[25]. All three arms will be included simultaneously in the Net Monetary Benefits (NMB) analyses without the need to specify the comparator[26]. The NMB will be obtained by multiplying the willingness to pay thresholds by the difference between the mean QALYs and

mean costs for each comparator. The NMB values will be calculated at thresholds between £5k and £60k.

At each threshold, 2000 bootstrap model iterations of the NMB adjusted for baseline covariates including baseline utility will be conducted to generate the cost-effectiveness planes/ellipses and associated cost-effectiveness acceptability curves (CEACs). The arm with the highest net benefit has the highest probability of being cost-effective. CEACs will graphically show the probability of one arm being the most cost-effective alternative compared to the other two arms over a range of willingness-to-pay thresholds[27]. Deterministic sensitivity analyses will be undertaken to look at the three sources of methodological uncertainty; societal perspective, intervention costs and the various ways of estimating the costs associated with length of stay. A secondary analysis will be performed to take into account the impact of the intervention 24 hours post-surgery. The primary outcome (VAS pain score during movement at 24 hours) will be used to predict EQ-5D-5L scores at 24 hours which will constitute an additional data point to estimate QALYs using linear interpolation between all time points.

13. Trial supervision

13.1 Trial Steering Committee

The TSC will consist of an independent chair, professionals with relevant clinical and academic experience and one patient representative. The role of the TSC is to provide supervision of the protocol, and statistical analysis plan, to provide advice on and monitor the study, to review information from other sources and consider recommendations from the DMEC. The TSC will meet at regular intervals, as defined in the TSC terms of reference.

13.2 Data Monitoring and Ethics Committee

The DMEC will review reports provided by the CTRU to assess the progress of the study, the safety data and the critical endpoint data as required. The DMEC will meet at regular intervals, as defined by the DMEC charter.

13.3 Trial Management Group

The Trial Management Group (TMG) is comprised of the CI, trial manager, statistician, data manager, Sponsor representative and grant co-applicants. PIs will also be invited to represent

sites. The CI will chair monthly meetings with the TMG to discuss the day-to-day implementation of the study.

14. Data handling and record keeping

Participant confidentiality will be respected at all times and the principles of the UK Data Protection Act (DPA) will be followed. The investigator will ensure that identifiable data is kept securely and protected from unauthorised parties.

Data management will be provided by the University of Sheffield Clinical Trials Research Unit (CTRU) who adhere to their own Standard Operating Procedures (SOPs) relating to all aspects of data management, including data protection and archiving. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP (Shef/CTRU/DM009).

The investigator or delegate at each site will maintain comprehensive and accurate source documents to record all relevant study information regarding each participant. All participants will be assigned a unique study ID number at screening that will link all of the clinical information collected for them on the study database. It will also be used in all correspondence between CTRU and participating centres. All CRFs will only identify the participant by their study ID number.

Study records, including source data, will be stored for 25 years after the completion of the study by participating sites, before being destroyed. Each investigator is responsible for ensuring records are retained and securely archived during the retention period and information supplied to the Chief Investigator and Sponsor. Where trial related information is documented in the medical records, those records will be retained for at least 25 years after the last patient last visit. Access will be restricted to authorised individuals.

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (CTRU SOP PM012) for 25 years following completion. Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for a minimum of 25 years to ensure that access is future-proofed against changes in technology.

Electronic data may also be stored (e.g. on a compact disc or USB flash drive) with the paper files. Archived documents will be transferred to the Sponsor before destruction.

14.1 Archiving

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (*SOP PM012 Archiving*). Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for the period stated above.

15 Data access and quality assurance

The study will use the CTRU's in-house data management system (Prospect) for the capture and storage of study specific participant data. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive access management feature will be used to ensure that users have access to only the minimum amount of data required to complete tasks relevant to their study role. This feature can also be used to restrict access to personal identifiable data.

The research staff at each site will enter data from source documents into the study specific Prospect database when available. After data has been entered, electronic validation rules are applied to the database on a regular basis; discrepancies are tracked and resolved through the Prospect database. All entries and corrections are logged with the person, date and time captured within the electronic audit trail.

Participant confidentiality will be respected at all times. All research data will be anonymised, and will only be identifiable by the participant's study ID number. No patient identifiable data will be transferred from the database to the statistician. Participating investigators shall agree to allow study-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this will be obtained as part of the consent process.
Further details on Data Management can be found in the trial Data Monitoring Plan (DMP).

15.1 Site assessment

Throughout this protocol, the trial 'site' refers to the hospital at which trial-related activities are conducted. Participating sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (clinical trials) Act (SI 2004/1031 and all amendments)
- Data collection requirements

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up to date, and copies held in the Investigator Site File (ISF), and the Trial Master File (TMF). Staff should also have completed GCP training within the last three years, ensure this is renewed every three years, and copies of the GCP certificate are held within the ISF and TMF.

Before each site is activated, capability to conduct the trial will be assessed and documented using a site assessment form. The CTRU will arrange a site initiation with each site, which may be carried out face-to-face or remotely. Site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Once all the required documentation is in order and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation, and should be willing and able to take steps to avoid unintentional unblinding before site activation.

15.2 Risk Assessment

A risk assessment has been performed by the CTRU, in accordance with Sheffield CTRU Standard Operating Procedures. The study has been categorised as MHRA Type B. The level of risk has been agreed with the Sponsor.

Central and/or on-site monitoring (including Pharmacy) will be undertaken at a level appropriate to the detailed risk assessment, and will be documented in the Site Monitoring Plan (SMP).

15.3 Reporting serious breaches and non-compliances

A “serious breach” is a breach of either: the conditions and principles of GCP in connection with the trial or; the protocol relating to the trial; which is likely to effect to a significant degree

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition may apply during the trial conduct phase. The sponsor of a clinical trial will notify the REC and, for CTIMPs, the MHRA in writing within 7 days of becoming aware of a serious breach.

All serious breaches and protocol non-compliances should be reported to CTRU within 24 hours of site staff becoming aware.

15.4 On-site monitoring

On-site or remote monitoring will be performed according to the monitoring plan and in line with the Sheffield CTRU Site Monitoring SOP (*SOP QA001 Site Monitoring).*

Regular site monitoring visits will occur throughout the study as specified in the Site Monitoring Plan and additional visits will be undertaken where required. At these visits, the Monitor will review activity to verify that the:

1. Data are authentic, accurate and complete.
2. Safety and rights of the patient are being protected and
3. Study is conducted in accordance with the approved protocol and study agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against Investigator's records by the Study Monitor (source document verification) (see section 13 for further details on data collection). Study Monitor will contact and visit sites regularly to inspect CRFs throughout the study, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered on the CRFs. Monitoring visits will also include a pharmacy visit to review processes, documentation and accountability of study drug.

A close-out visit will be performed after the last patient last visit at each site. Further close-out activities may be carried out remotely after this time, up to database freeze.

15.5 Central monitoring

CTRU staff will review entered data for possible errors and missing data points. A central review of consent forms will also be completed, and sites will be requested to share consent forms with CTRU via a study specific NHS.net account on an ongoing basis. This will be made clear to the participant prior to their consent to the trial. CTRU will receive pharmacy dispensing logs centrally, which will be taken to on-site monitoring visits to allow full source data verification. Details will be included in the IMP and Pharmacy manual.

Monitors should continue to check sites processes in relation to maintaining blinding/accidental unblinding early in the trial and periodically thereafter, either through central or on-site monitoring.

15.6 Regulatory information

As a CTIMP, the trial will be conducted in accordance with ICH GCP and the Clinical Trials and Medicine for Human Use (Clinical Trials) Regulations 2004.

16. Publication

Results of the study will be disseminated through peer reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the study will also be made available on the Sheffield CTRU website. Summaries of the research will be updated periodically to inform readers of ongoing progress.

The results will be published on a freely accessible database within one year of completion of the trial.

Full details, including guidance on authorship, are documented in the Publication and Dissemination Plan.

17. Finance

This project (NIHR153170) is funded by the Health Technology Assessment (HTA) Programme and details have been drawn up in a separate agreement. Further details are included in the collaborator agreement.

18. Ethics approval

Before initiation of the study at participating site, the protocol, informed consent forms and information materials to be given to the participants will have received NHS Research Ethics Committee approval. The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and ICH GCP. NHS REC and MHRA approval will be sought before the start of the trial. Protocol amendments, once approved by the funder, the MHRA (where applicable) and the REC, will be communicated to study staff and R&D offices by Sheffield CTRU. An agreement between the Sponsor, participating site and CTRU will outline responsibilities of all parties and be signed prior to recruitment start. All persons responsible for recruiting patients will be required to complete Good Clinical Practice (GCP) training.

The study will be submitted to local participating Trusts to confirm Capacity and Capability before any research activity takes place.

19. Regulatory Compliance

To demonstrate that the trial will comply with regulations, the trial will also not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA and Favourable REC opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

20. Sponsor and site approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will receive sponsor approval.

A site agreement between the Sponsor and participating sites outlines responsibilities of all parties and will be signed prior to commencement of recruitment at each site.

Recruitment of study participants will not commence at a site until a letter of local R&D Confirmation of Capacity and capability (CCC) has been issued, and Sheffield CTRU have provided site green light on behalf of the sponsor.

21.Trial Organisation and Responsibilities

21.1 Principal Investigators and Co-Investigators

Each site will have a local Principal Investigator (PI) who will be delegated responsibility for the conduct of research at their centre and must sign a declaration to acknowledge these responsibilities. The local PI should ensure that all relevant staff involved are well informed about the trial and trained in study procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI will liaise with the Trial Manager on logistic and administrative matters connected with the trial. Due to the dual aspect nature of the trial, involving combined skills from both spinal surgeons and anaesthetists, it is suggested that each site has a delegated co-investigator to support the principal investigator. Each site should have a dyad investigator team including one anaesthetist and one spinal surgeon for appropriate coordination; however, there can only be one delegated principal investigator who takes overall responsibility for the trial locally.

21.2 Sheffield Clinical Trials Research Unit (CTRU)

The Sheffield CTRU at Sheffield University will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Policy Framework for Health and Social Care Research 2017. CTRU responsibilities include randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support the main REC, HRA and site-specific submissions, clinical set-up, on-going management including training, monitoring reports and promotion of the trial.

The CTRU trial manager will be responsible for supplying investigator and pharmacy site files to each collaborating centre after relevant ethics committee approval and local R&D Confirmation of Capacity and Capability approval has been obtained. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU will develop the site monitoring plan and data management plan and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of noncompliance.

22. Patient & Public Involvement

A patient and public involvement group has been established, comprising of a small group of patients who have previously undergone lumbar spine surgery. The group have met twice during the development of this trial and will continue to provide input throughout the trial, commenting on patient facing materials and assisting with the dissemination of results and other information to patients and the public. PPI members will be invited to attend TMG and TSC meetings to input into the running of the trial, and will contribute during the write-up period to ensure the needs of a service user audience are met.

23. Indemnity / Compensation / Insurance

The University of Sheffield has in place clinical trials insurance against liabilities for which it may be legally liable, and this cover includes any such liabilities arising out of this clinical study. Standard NHS indemnity operates in respect of the clinical treatment which is provided.

24. References

1. Wang J, Sun H, et al. Efficacy and safety of intrathecal morphine for pain control after spinal surgery: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2021 Mar;25(6):2674–84.
2. Pendi A, Acosta FL, et al. Intrathecal Morphine in Spine Surgery: A Meta-analysis of Randomized Controlled Trials. Spine . 2017 Jun 15;42(12):E740–7.
3. Geisler A, Zachodnik J, Køppen K, Chakari R, Bech-Azeddine R. Postoperative pain treatment after spinal fusion surgery: a systematic review with meta-analyses and trial sequential analyses. Pain Rep. 2022 May;7(3):e1005.
4. Ivanusic J, Konishi Y, Barrington MJ. A Cadaveric Study Investigating the Mechanism of Action of Erector Spinae Blockade. Reg Anesth Pain Med. 2018 Aug;43(6):567–71.
5. Schwartzmann A, Peng P, et al. A magnetic resonance imaging study of local anesthetic spread in patients receiving an erector spinae plane block. Can J Anaesth. 2020 Aug;67(8):942–8.
6. Yang HM, Choi YJ, Kwon HJ, O J, Cho TH, Kim SH. Comparison of injectate spread and nerve involvement between retrolaminar and erector spinae plane blocks in the thoracic region: a cadaveric study. Anaesthesia. 2018 Oct;73(10):1244–50.
7. Duan M, Xu Y, Fu Q. Efficacy of Erector Spinae Nerve Block for Pain Control After Spinal Surgeries: An Updated Systematic Review and Meta-Analysis. Front Surg. 2022 Feb 28;9:845125.
8. Liu MJ, Zhou XY, Yao YB, Shen X, Wang R, Shen QH. Postoperative Analgesic Efficacy of Erector Spinae Plane Block in Patients Undergoing Lumbar Spinal Surgery: A Systematic Review and Meta-Analysis. Pain Ther. 2021 Jun;10(1):333–47.
9. Kang R, Chin KJ, et al. Bilateral single-injection erector spinae plane block versus intrathecal morphine for postoperative analgesia in living donor laparoscopic hepatectomy: a randomized non-inferiority trial [Internet]. Regional Anesthesia & Pain Medicine. 2019. p. rapm – 2019. Available from: http://dx.doi.org/10.1136/rapm-2019-100902
10. Hamed MA, Yassin HM, et al. Analgesic Efficacy of Erector Spinae Plane Block Compared with Intrathecal Morphine After Elective Cesarean Section: A Prospective Randomized Controlled Study. J Pain Res. 2020 Mar 24;13:597–604.
11. Avis G, Gricourt Y, Vialatte PB, Meunier V, Perin M, Simon N, et al. Analgesic efficacy of erector spinae plane blocks for lumbar spine surgery: a randomized double-blind controlled clinical trial. Reg Anesth Pain Med. 2022 Oct 1;47(10):610–6.

12. Daabiss M. American Society of Anaesthesiologists physical status classification. Indian J Anaesth. 2011 Mar;55(2):111–5.
13. Myles PS, Myles DB, et al. Measuring acute postoperative pain using the visual analog scale: the minimal clinically important difference and patient acceptable symptom state. Br J Anaesth. 2017 Mar 1;118(3):424–9.
14. Herdman M, Gudex C, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727–36.
15. Stark PA, Myles PS, et al. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. Anesthesiology. 2013 Jun;118(6):1332–40.
16. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. Physiotherapy. 1980 Aug;66(8):271-3. PMID: 6450426.
17. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Arch Intern Med. 2006 May 22;166(10):1092–7.
18. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001 Sep;16(9):606–13.
19. Cook JA, Bruckner T, MacLennan GS, Seiler CM. Clustering in surgical trials--database of intracluster correlations. Trials. 2012 Jan 4;13:2.
20. Howard DR, Brown JM, Todd S, Gregory WM. Recommendations on multiple testing adjustment in multi-arm trials with a shared control group. Stat Methods Med Res. 2018 May;27(5):1513–30.
21. Parker RA, Weir CJ. Non-adjustment for multiple testing in multi-arm trials of distinct treatments: Rationale and justification. Clin Trials. 2020 Oct;17(5):562–6.
22. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ. 2011 Feb 7;342:d40.
23. Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. Value Health. 2015 Mar;18(2):161–72.
24. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ. 2005 May;14(5):487–96.
25. Faria R, Gomes M, et al. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. Pharmacoeconomics. 2014

Dec;32(12):1157–70.

26. Briggs AH, Claxton K, Sculpher MJ. Decision Modelling for Health Economic Evaluation. Oxford University Press; 2006. 237 p.
27. Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. Annu Rev Public Health. 2002;23:377–401.