

1. Protocol Details

1.1 Protocol Title:

Preoperative paravertebral block in cancer surgery of the lung: ParaSOL a prospective randomised controlled clinical trial

1.2 Names (Titles), titles and contact details of:

Sponsor

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1.3 Protocol Details

Version number	1.0
Final/draft	Final
Date	11/07/2019

2. Signature Page

The Chief Investigator and the R&D (sponsor office) have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Dr Cheng Ong

Signature

Date

Sponsor Representative

GSTFT

Signature

Date

This Protocol template is intended for use with UK sites only.

3. List of Abbreviations and Definitions

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

4. Summary/Synopsis

Title	Preoperative paravertebral block in cancer surgery of the lung: ParaSOL a prospective randomised controlled clinical trial
Protocol Short Title/Acronym	ParaSOL
Protocol Version number and Date	V0.1 28/06/2019
Is the study a Pilot?	No
IRAS Number	244767
REC Reference	
Study Duration	24 months
Methodology	<i>Double-blind randomised controlled study</i>
Sponsor name	Guy's and St Thomas' NHS Foundation Trust
Chief Investigator	Dr Cheng Ong
Funder Name	European Society of Regional Anaesthesia (ESRA)
Medical condition or disease under investigation	Paravertebral analgesia in lung cancer surgery
Purpose of clinical trial	Does the contribution of a preemptive preoperative ultrasound-guided paravertebral analgesic blockade (PVB) 'pre-PVB LA', administered in addition to a postoperative PVB local anaesthetic infusion 'post-PVB LA', reduce the severity of acute postoperative pain?
Primary objective	The primary outcome is the proportion of patients with clinically relevant moderate-to-severe pain (NRS ≥ 3) related to the surgical site at rest at 24h
Secondary objective (s)	Secondary outcomes are acute pain as measured by NRS, cumulative 48h morphine requirement, mobilization, respiratory and in-hospital complications, length of hospital stay, quality of life and chronic post-surgical pain (CPS).P.
Number of Subjects/Patients	100 subjects
Trial Design	<p><u>Population:</u> Adults ≥ 18 years of age, having elective primary lung cancer surgery by video-assisted thoracoscopy for a single lobectomy</p> <p><u>Intervention:</u> After general anaesthesia, but before surgery, ultrasound-guided pre-PVB injection will be performed by the anaesthetist.</p> <p>The pre-PVB injectate will be 20ml 0.5% levobupivacaine (pre-PVB LA).</p> <p>At the end of surgery, the surgeon will administer a standard post-PVB LA injection and infusion.</p>

	<p><u>Comparison:</u> After general anaesthesia, but before surgery, ultrasound-guided pre-PVB injection will be performed by the anaesthetist.</p> <p>The pre-PVB injectate will be 20ml normal saline (pre-PVB saline).</p> <p>At the end of surgery, the surgeon will administer a standard post-PVB LA injection and infusion.</p>
Endpoints	<p>PRIMARY OUTCOME</p> <ol style="list-style-type: none"> 1. The proportion of patients with clinical relevant moderate-to-severe pain (NRS ≥ 3) related to the surgical site at rest at 24h (1). <p>SECONDARY OUTCOMES</p> <ol style="list-style-type: none"> 1. Acute postoperative pain related to the surgical site as measured by a numerical rating scale (NRS) at rest and on coughing, preoperatively, and after arrival in recovery at 1, 6, 24 and 48h (2). 2. Cumulative morphine requirement over 48h post arrival in recovery. 3. Time to first mobilization (walking 50m without the aid of another person), measured at baseline pre-operatively and postoperatively on daily assessment. 4. Incidence of in-hospital complications (AF, MI, unplanned ICU admission) and respiratory complications, as defined by the Melbourne Group Scale (3). 5. Length of hospital stay 6. Quality of life (QoL) score at pre-operative assessment, 3 and 6 months postoperatively as measured by the EORTC-QLQ-C30 version 3 (4–6). 7. Presence of chronic post-surgical pain (CPSP) (binary yes/no) fulfilling CPSP criteria at 3 and 6 months post-surgery as assessed by DN4 (7–9).
Main Inclusion Criteria	<ul style="list-style-type: none"> • Elective radical primary lung cancer VATS surgery for single lobectomy • ASA I-III • Age ≥ 18
Main Exclusion Criteria	<ul style="list-style-type: none"> • Planned open thoracotomy, wedge resection, bilobectomy, pneumonectomy, chest wall resection or total pleurectomy

	<ul style="list-style-type: none"> • Local anaesthetic or opioid allergy • Coagulation disorders • Inability to comply with study questionnaire completion • Pre-existing pain in chest area or pre-existing pain conditions • Local infection/tumour at proposed PVB site • Previous lung surgery • Planned surgery within 3 months of the primary lung resection
Statistical Methodology and Analysis	<p>Baseline risk factors and demographics of the overall study participants will be reported, stratified by their treatment allocation group in accordance to CONSORT guidelines. Patient outcomes will be analysed according to intention-to-treat.</p> <p>Primary outcome:</p> <p>The proportion of patients with clinically relevant moderate-to-severe pain (Numerical Rating Scale [NRS] ≥ 3) related to the surgical site at rest at 24h in treatment (pre-PVB LA) and control (pre-PVB saline) arms will be compared using the chi-square test for equality of two proportions</p> <p>Secondary outcomes:</p> <p>For all secondary outcomes, the distributions of outcome variables will be assessed for normality. To compare outcomes between treatment and control arms, we will use Student's t test to for normally-distributed continuous outcome variables, the Mann-Whitney test for non-normally distributed continuous and ordinal outcome variables, and chi-square tests for binary outcome variables.</p>

5. Introduction

In the UK, there has been an increase in lung cancer operations, especially in high risk and elderly patients, improving survival from 10.6% in 2008 to 15.1% in 2013 (10–13). Lung cancer surgery is associated with severe acute pain, a high incidence of respiratory complications and chronic post-surgical pain (CPSP)(3). Severe acute postoperative pain is a strong predictor of CPSP (14–17). The improvement of perioperative outcomes in elderly patients, the benefits of regional anaesthesia and reduction of chronic pain are investigative priorities of the Anaesthesia and Perioperative Care Setting Partnership (18).

Enhanced recovery strategies include video-assisted thoracoscopic surgery (VATS), a minimally invasive alternative to open thoracotomy, which may be associated with less postoperative pain (11,15,19–21). Regional anaesthesia, by thoracic epidural analgesia (TEA) or paravertebral analgesic blockade (PVB) is superior to systemic opioids in reducing acute pain after thoracotomy surgery (22–27).

Preemptive analgesia describes the aim of minimizing central spinal pain transmission by noxious stimuli arising from events at surgery, by administering an analgesic technique prior to surgical incision (28,29). Regional blockade affects central sensitization, allowing analgesia to outlast the

pharmacological sensory blockade (29).

Compared to TEA initiated after surgery, acute pain severity is reduced by preemptive TEA (30). There are conflicting reports on the benefit of preemptive analgesia in other types of surgery (23,28–31), but TEA and PVB may prevent CPSP in thoracotomy and breast surgery (32). Some small studies have shown that pre-PVB reduces acute postoperative pain (24,33,34).

Paravertebral blockade is known to be as effective as TEA for acute postoperative analgesia following thoracic surgery, whilst having a lower incidence of pulmonary complications, hypotension and nausea (26,27). It is conventional practice in many centres for the surgical administration and placement of a catheter at the end of surgery for postoperative LA infusion (post-PVB) as the sole method of regional analgesia (35). Preoperative PVB is less common: anaesthetists may use a landmark technique, single or multiple injections and different volumes/strengths of LA (24,33,34,36–38).

Ultrasound guidance for pre-PVB injection increases accuracy (39,40). In an audit using this technique with post-PVB compared to post-PVB only, we demonstrated reduced pain numerical rating scale (NRS) scores in elective VATS patients, (mean NRS at 24h 2.5 vs 4.5), and a reduction in the proportion of patients who experienced moderate-to-severe pain of NRS ≥ 3 from 83% to 50% at 24h (41).

We therefore aim to evaluate the contribution of ultrasound-guided pre-PVB, administered in addition to the post-PVB LA infusion, in reducing the severity of acute postoperative pain, perioperative opioid requirement, development of CPSP, and improving patient outcome in lung cancer patients undergoing VATS.

6. Trial Objectives and purpose

Study Aim

We aim to determine whether ultrasound-guided preemptive PVB local anaesthetic (pre-PVB LA), administered in addition to the post-operative PVB (post-PVB) local anaesthetic (LA) infusion, reduces acute postoperative pain, opioid requirement, chronic pain, and improves surgical recovery, in thoracoscopic surgery for lung cancer.

PRIMARY OUTCOME

1. The proportion of patients with clinical relevant moderate-to-severe pain (NRS ≥ 3) related to the surgical site at rest at 24h (1).

SECONDARY OUTCOMES

1. Acute postoperative pain related to the surgical site as measured by a numerical rating scale (NRS) at rest and on coughing, preoperatively, and after arrival in recovery at 1, 6, 24 and 48h (2).
2. Cumulative morphine requirement over 48h post arrival in recovery.
3. Time to first mobilization (walking 50m without the aid of another person), measured at baseline pre-operatively and postoperatively on daily assessment.
4. Incidence of in-hospital complications (AF, MI, unplanned ICU admission) and respiratory complications, as defined by the Melbourne Group Scale (3).
5. Length of hospital stay
6. Quality of life (QoL) score at pre-operative assessment, 3 and 6 months postoperatively as measured by the EORTC-QLQ-C30 version 3 (4–6).
7. Presence of chronic post-surgical pain (CPSP) (binary yes/no) fulfilling CPSP criteria at 3 and 6 months post-surgery as assessed by DN4 (7–9).

7. Study Design & Flowchart

7.1 Study Design

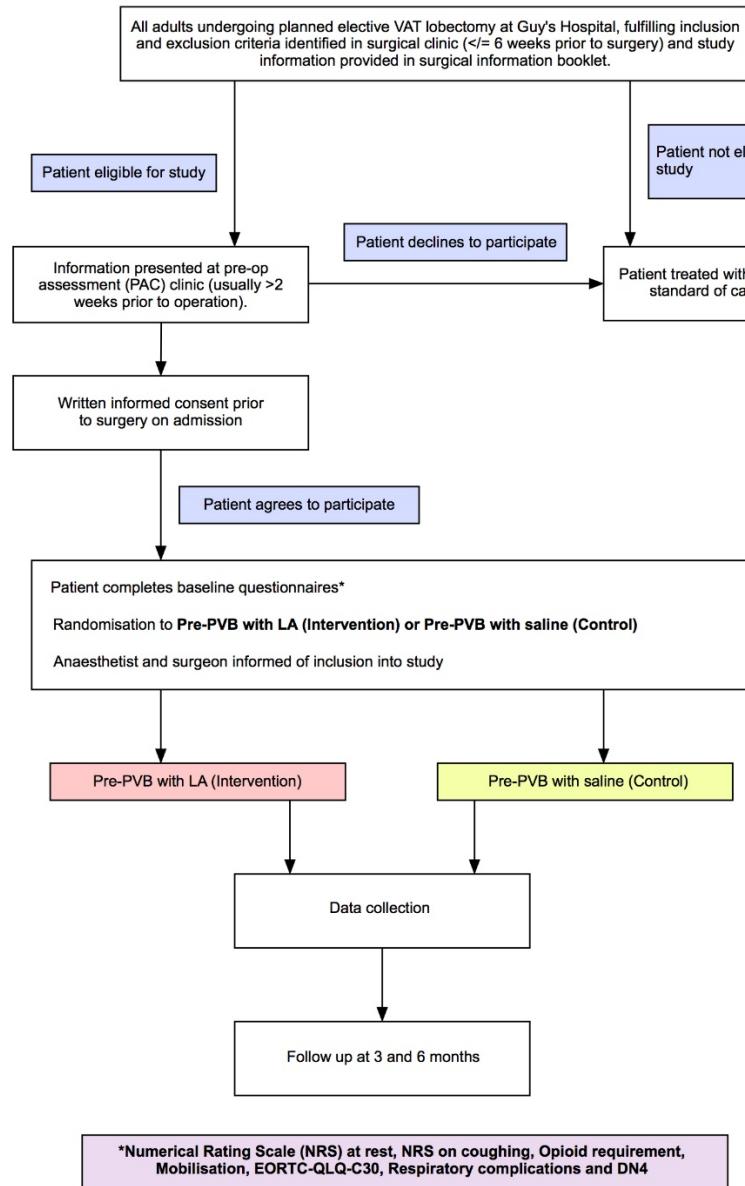
EXPERIMENTAL DESIGN (Table 1)

Table 1 ParaSOL in PICOT Format

Research question	<p>ParaSOL is a double-blinded randomised controlled trial investigating the question:</p> <p>Does the contribution of a preemptive preoperative ultrasound-guided PVB ‘pre-PVB LA’, administered in addition to a postoperative PVB local anaesthetic infusion ‘post-PVB LA’, reduce the severity of acute postoperative pain?</p>
Population	Adults ≥18 years of age, having elective primary lung cancer surgery by video-assisted thoracoscopy for a single lobectomy
Intervention	<p>After general anaesthesia, but before surgery, ultrasound-guided pre-PVB injection will be performed by the anaesthetist.</p> <p>The pre-PVB injectate will be 20ml levobupivacaine (pre-PVB LA).</p> <p>At the end of surgery, the surgeon will administer a standard post-PVB LA injection and infusion.</p>

Comparison	<p>After general anaesthesia, but before surgery, ultrasound-guided pre-PVB injection will be performed by the anaesthetist.</p> <p>The pre-PVB injectate will be 20ml normal saline (pre-PVB saline).</p> <p>At the end of surgery, the surgeon will administer a standard post-PVB LA injection and infusion.</p>
Outcome	<p>The primary outcome is the proportion of patients with clinically relevant moderate-to-severe pain (NRS ≥ 3) related to the surgical site at rest at 24h</p> <p>Secondary outcomes are acute pain as measured by NRS, cumulative 48h morphine requirement, mobilization, respiratory and in-hospital complications, length of hospital stay, quality of life and CPSP.</p>
Time	Data collection will be until 6 months after surgery

Fig 1 Flow of participants in the trial



Our study is a parallel group design of a control and intervention group. The anticipated journey of participants through the trial is illustrated in Fig 1. Both study groups will receive a preoperative paravertebral block injection after general anaesthesia and before surgery, and a local anaesthetic paravertebral block injection and infusion at the end of surgery. Only the intervention group will be administered a local anaesthetic preoperative paravertebral block injection; the control group will be administered a saline placebo preoperative paravertebral injection.

The paravertebral infusion will be managed as per standard Trust protocol. The data collection will continue with follow-up after the participant is discharged from hospital for 6 months after the date of surgery. It is conventional to follow-up patients for at least 6 months for pain and pain related outcomes when studying the incidence of chronic pain. Adverse events will be collected throughout the study period.

Table 3 Study assessments

Assessments	Pre-operative baseline	Intra-operative	Post-operative Hours 1 6 24 48	Follow-up Hospital		
				Discharge	3 months	6 months
Pain NRS at rest	X	...	X X X X	...	X	X
Pain NRS on coughing	X	...	X X X X	...	X	X
Opioid requirement	X	X	X X X X	...	X	X
Mobilisation	X X X
EORTC- QLQ-C30	X	X	X
Respiratory and in-hospital complications	X	...	X	X
DN4	X	X	X

8. Subject Selection

This single-centre study will be conducted at Guy's Hospital, a large tertiary thoracic centre for London, Sussex, Kent and Berkshire. In 2015, 459 lung cancer resection operations were performed; 8% of all lung cancer resections in England (42).

The source of subjects are adults presenting for elective primary lung cancer surgery, by video-assisted thoracoscopy (VAT) for a single lobectomy. We chose to study only those participants who would be chosen by standard surgical criteria as suitable for VAT or key-hole surgery, and not to include open thoracotomy patients (a much bigger surgical incision and trauma), because pain outcomes are likely to be influenced by the surgical incision. A VAT procedure is commonly practised at our centre, with the intention of improving postoperative recovery in lung cancer

patients. It is the procedure of choice over an open thoracotomy.

Our unit performed 350 VAT lung cancer resections in 2016. We estimate that 50% (175) will be eligible from our study criteria, and agreement to recruitment to be 60% (105). We envisage that recruitment will take at least 12 months with a conservative estimate of 18 months, with final six-month follow-up at 24 months.

8.1 Subject Inclusion Criteria

Inclusion Criteria

- Elective radical primary lung cancer VATS surgery for single lobectomy
- ASA I-III
- Age ≥ 18

8.2 Subject exclusion criteria (with justification if necessary – for example consider contraindications to trial treatments, incompatible concurrent treatments, recent involvement in other research)

Exclusion Criteria

- Planned open thoracotomy, wedge resection, bilobectomy, pneumonectomy, chest wall resection or total pleurectomy
- Local anaesthetic or opioid allergy
- Coagulation disorders
- Inability to comply with study questionnaire completion, and non-English speakers
- Pre-existing pain in chest area or pre-existing pain conditions
- Local infection/tumour at proposed PVB site
- Previous lung surgery
- Planned surgery within 3 months of the primary lung resection

Criteria for discontinuation/withdrawal or modifying allocated treatment:

- Participant request to withdraw from the study.
- Intraoperative identification of infection/tumour in paravertebral space

The exclusion of pre-existing pain in the chest area pre-existing conditions is consistent with the 2016 IMMPACT research design recommendations for chronic pain trials.

9. Study Procedures

9.1 Subject Recruitment

Eligible patients will be identified in the catchment outpatient clinics 4-6 weeks before surgery by the direct care team. The participant information sheet (PIS) will be introduced in the standard surgical booklet given by the surgeon (see appendix), further supported by a web resource link. Participation will be completely voluntary, and the participants will not be paid.

At the preoperative assessment clinic 2-3 weeks before surgery, a face-to-face discussion with the research nurse will support the PIS; the opportunity to ask any questions and contact a member of the research team will be given. The subject will therefore have this period until their admission to decide to take part. At the discussion, those patients that lack capacity to comply with questionnaire completion will be excluded from the trial.

Sufficient time will be given to discuss and ask any questions before taking consent. If the patient consents to participate in the study, written informed consent will be obtained, by a member of the research team prior to or on the day of surgery. If the patient decides to enter the trial, they will be asked to sign two original copies of the consent form; a research team member will countersign the form. The patient will retain one original copy of the signed consent form, and the second original copy will be photocopied. The photocopy will be kept in the patient medical records, and the original will be kept in the Investigator site file. A letter will be sent to the patient's GP to inform them about the study (see appendix).

9.2 Screening Procedures

Patients will be identified by standard surgical criteria, by the surgeons, for elective lung cancer resection of a single lobe by VAT, at the outpatient clinics.

The research team will use the inclusion and exclusion criteria to determine the eligible patients, and entered into the screening log. The research nurse will be authorized to complete this task.

9.3 Randomisation Procedures

Participants will be randomised on the day of surgery to the 'pre-PVB LA' or 'pre-PVB saline' arm, by a study investigator, with a 1:1 randomisation ratio using 'Castor EDC' online software. Each subject will receive a unique randomization code in an envelope that will only be opened during the preparation of the pre-PVB injectate.

9.4 Masking & other measures taken to avoid bias

9.4.1 Masking

Blinding of allocations:

A non-blinded research nurse, will prepare the pre-PVB injectate in a standard syringe according to the allocation, labelled by participant number, in a theatre location concealed from the operating room and staff. The local anaesthetic will be taken from standard theatre pharmacy stock. ParaSOL is not a Medicines for Human Use Trial (non-CTIMP).

The anaesthetist, the surgeon and theatre team, recovery staff, and the researchers performing all the outcome assessments will be separate and blinded to the group allocation. The intervention LA injectate is identical in appearance to the placebo injectate of saline (identical placebo). After the operation, the PVB catheter will be taped as normal before connecting the standard post-PVB LA

infusion pump, and no visible difference will be seen by the patient.

We have elected to perform an interventional placebo intervention as opposed to a sham control to minimize observer bias. The main risk of pre-PVB saline insertion, pneumothorax, is insignificant to the chest surgery.

On occasions where patient safety relies on it (e.g. suspected LA side effects), unblinding will be permissible by protocol.

9.5 Schedule of Treatment of each Visit

The interventions will take place at a single hospital admission for the participant and two follow-up episodes at 3 and 6 months (Table 3).

Assessments	Pre-operative baseline	Intra-operative	Post-operative Hours 1 6 24 48	
Pain NRS at rest	X	...	X X X X	
Pain NRS on coughing	X	...	X X X X	...
Opioid requirement	X	X	X X X X	...
Mobilisation	X X X	...
Respiratory and in-hospital complications	X	...	X	X

Preoperative assessment:

The patient will be evaluated by a study investigator at the beginning of their hospital stay after routine admission procedures on the ward.

Conduct of Anaesthesia

Patients will be anaesthetised by experienced consultant thoracic anaesthetists who regularly perform PVB, trained by supervised practice, practical workshops, and adherence to the Trust PVB guideline.

For all patients, AAGBI standard monitoring and BIS monitoring will be applied at the start of anaesthesia. Patients will be preoxygenated and fentanyl $1 \mu\text{g kg}^{-1}$, propofol target-controlled infusion targeting a BIS value of 40-60, and rocuronium 0.5 mg kg^{-1} will be administered.

After general anaesthesia, participants will be placed in the lateral operative position and the pre-PVB injection will be performed by the anaesthetist. Using a transversal in-plane technique, 10ml of pre-PVB study injectate will be administered each at T3/4 and T7/8 levels using a 18G Sonoplex 100mm Tuohy needle (39).

Standard perioperative analgesia is shown in Table 2.

Table 2 Standardised analgesia

	Analgesia according to hospital protocol
Intraoperative	Paracetamol 1 g IV Fentanyl IV, unrestricted supplementation allowed Surgically-placed post-PVB LA and infusion: 30ml 0.25% levobupivacaine and 0.125% plain bupivacaine 3-10 ml/h
Recovery analgesia	Morphine IV boluses 2mg every 5 min Morphine IV PCA 1mg bolus, 5 min lockout PVB infusion continued
Postoperative analgesia	Morphine IV PCA Paracetamol 1 g 6hrly Ibuprofen 400mg 8hrly if not contraindicated PVB infusion continued until 4h after chest drain removal Morphine immediate release tablets 10 mg PRN when PCA discontinued

Conduct of surgery

VATS will be performed via the standard surgical technique, the Copenhagen approach, which is 3-4 surgical port incisions at T4-8, and a single 28F chest drain in the T7/8 intercostal space (43).

Surgical Post-PVB

In both study groups, before final wound closure, the surgeon will administer a post-PVB LA injection using a 18G Tuohy needle, and introduce a catheter under direct vision, followed by LA infusion (Table 2) (44) . We deem placement of catheters by this method to be superior to ultrasound-guided placement (40). Chest drains will be removed according to standard indications (no air leak, output <400ml/24h, no active bleeding or chylothorax), and the post-PVB will be continued until 4h afterwards.

9.6 Follow Up Procedures

Timing of study assessments are shown in Table 3. After discharge, the standard questionnaires will be performed by phone (supported by reminder letter/email) to minimise disruption to the patient, at 3 months and 6 months after surgery.

	Follow-up:	
	3 months	6 months
Pain NRS at rest	...	X
Pain NRS on coughing	X	X
Opioid requirement	X	X
EORTC- QLQ-C30	X	X
DN4	X	X

9.8 End of Study Definition

The end of the study is marked by the final 6 month follow-up of the final participant.

10. Assessment of Safety

10.1 Definitions

Term	Definition
Adverse Event (AE)	<p>Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons</p> <p>Note 1: Local bleeding from the insertion of a paravertebral needle or catheter will not be classified as an adverse event. Local anatomical spread of the local anaesthetic will not be classified as an adverse event.</p>
Serious Adverse Event (SAE)	<p>Any adverse event that:</p> <ul style="list-style-type: none"> • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in <ul style="list-style-type: none"> • a life-threatening illness or injury, or • a permanent impairment of a body structure or a body function, or • in-patient or prolonged hospitalisation, or • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, <p>Note 2: Planned hospitalisation for a pre-existing condition, or a procedure required by the CIP (clinical investigation plan), without serious deterioration in health is not considered a SAE.</p>

An adverse event does not include:

- Medical or surgical procedures; the condition that leads to the procedure is an adverse event.
- Pre-existing disease, conditions, or laboratory abnormalities present at the start of the study that do not worsen in frequency or intensity.
- The disease being studied, lung cancer, or signs/symptoms associated with the disease unless more severe than expected for the subject's condition.

10.1.1 Safety Reporting requirements and timelines

Please refer to Appendix 1 for further information with regards to Safety Reporting

Term	Reporter	Reported to	Reporting Timeline from awareness of the event
Adverse Event (AE)	Investigator	Sponsor	As agreed with sponsor
Serious Adverse Event (SAE)	Investigator	Sponsor	Immediately, no more than 24hrs of becoming aware of the event

10.2 Assessment of adverse events

10.2.1 Severity and Seriousness

Category	Definition
Mild	The adverse event does not interfere with the subjects daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the subjects routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	<p>The adverse event results in alteration, discomfort or disability which is clearly damaging to health</p> <p>Note: A severity rating of severe does not necessarily categorise the event as an SAE.</p>

Seriousness as defined for an SAE in section 10.1.1.

10.2.2 Causality

The assessment of relationship of adverse events to the study procedure and the investigational device will be a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

Category	Definition
Yes	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
No	There is no evidence of any causal relationship.

10.2.3 Expectedness

Category	Definition

<i>Expected</i>	An adverse event that is consistent with the information about the intervention listed in the Investigator Brochure or clearly defined in this CIP.
<i>Unexpected</i>	An adverse event that is not consistent with the information about the intervention listed in the Investigator Brochure

The reference document to be used to assess expectedness against the intervention is the IB. The CIP will be used as the reference document to assess disease related and/or procedural expected events.

10.2.4 *Investigator Responsibilities*

All AEs and SAEs will be recorded in the medical records and CRF following consent.

All SAEs will need to be reported to the sponsor on a SAE form unless stated in the CIP that some expected SAEs will not be reported to the sponsor, with a justification as to why they will not be reported.

The Chief or Principal Investigator will complete the sponsor's serious adverse event form and the form will be emailed to the sponsor R&D@gstt.nhs.uk immediately (or within 24 hours but certainly no later than 24 hours) of his / her becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible

You may choose not to report EXPECTED SAEs to the sponsor for example if they are expected to occur on a regular basis and offer no further new information to your safety profile. These events must continue to be recorded in the source data and CRF, however you may state that you will not complete an SAE form and forward it to the sponsor.

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, or an unrelated event. These reports will be provided immediately (or within 24hours) upon notification.

The investigator shall keep detailed records of all adverse events relating to the clinical trial which are reported to them by trial participants or users. The investigator shall document all relevant information on sponsor provided AE logs, SAE forms and DD forms.

All SAEs, SADEs should be reported to R&D@gstt.nhs.uk

10.3 Foreseeable Adverse Events

The intervention is the administration of the paravertebral local anaesthetic block, after the patient is under anaesthesia. An ultrasound scan is used to aid the correct site of administration of the block, and is an advance to increase safety, as well to increase the success of the block. This is performed by an anaesthetist experienced in the technique, which is accepted practice in many of the operations at our centre. There are two adverse events which may be anticipated:

1. Inadvertent spread of local anaesthetic (minor adverse event):

- to the opposite side via epidural spread as evidenced by numbness on the opposite side of the body

- cranial spread to cause a Horner's or Harlequin sign

Both these adverse events do not require treatment, above the management of a routine paravertebral infusion, and can occur routinely with conventional postoperative paravertebral infusions.

From our routine practice, these adverse events occur uncommonly. This will be recorded as an expected AE in the CRF, and will **not** be reported to the sponsor.

2. Local anaesthetic toxicity from intravascular injection or absorption from paravertebral space

This is a rare adverse event which can theoretically occur from the administered injection or the postoperative paravertebral infusion. There is a standard hospital protocol for treatment of suspected local anaesthetic toxicity which can be initiated in the event of haemodynamic instability. Our institution has had a long history (over two decades) of administration of paravertebral local anaesthetic infusions, but a case of toxicity has never been demonstrated in the thoracic surgery patient population. In the literature, though moderately high plasma levels of local anaesthetic have been demonstrated in children, symptoms and signs of toxicity have not been demonstrated.

This event will be recorded in the CRF as a serious AE and an AE form will be completed to be forwarded to the sponsor.

11.0 Ethics Reporting

Reports of related and unexpected SAEs should be submitted to the Main REC within 15 days of the chief investigator becoming aware of the event, using the NRES template. The form should be completed in typescript and signed by the chief investigator. The main REC will acknowledge receipt of safety reports within 30 days. A copy of the SAE notification and acknowledgement receipt should be sent to the R&D Directorate.

Any SAE's that are expected and do not require reporting for this study are described above in 10.1.

Ethics & Regulatory Approvals

Appropriate Sponsorship will be sought from Guy's and St Thomas' NHS Foundation Trust and REC and HRA approval will be sought from XXXX

12.0 Compliance and Withdrawal

12.1 Subject compliance

The intervention does not require active compliance from the patient, as the PVB is administered when the patient is under general anaesthesia.

12.2 Dropout / Withdrawal of Subjects

Subjects will be withdrawn from the trial if there is a loss of capacity, a refusal to proceed with the study, if the patient is admitted to the intensive care unit and is under sedation and therefore unable to comply with follow-up questionnaires.

In this case, the data collected will be kept, but further study data will not be collected.

12.3 Protocol Compliance

If there is a deviation from protocol it will be documented and reported to the sponsor.

In the unlikely event of a deviation, a report to the CI should be made immediately as to how to proceed. The CI will discuss the case with the research team in a meeting to review the response.

13 Data

13.1 Data to be collected

Assessments	Source of data (data form)	Baseline before surgery	Intra-operative	Post-operative Hours 1 6 24 48	Follow-up Hospital		
					Discharge	3 months	6 months
Eligibility and written informed consent	Patient notes (descriptive)	X					
Demographic data and medical history	Patient notes (descriptive)	X					
Randomisation	Database (binary)	X Day of surgery					

Paravertebral insertion data	Patient notes and procedure (descriptive)	X					
Intraoperative data	Patient notes (descriptive)	X					
Pain NRS at rest and coughing	Standard questionnaire (numeric)	X	...	X X X X	...	X	X
Opioid analgesic requirement	Patient notes (continuous)	X	X	X X X X	...	X	X
Mobilisation (Time to standard distance)	Patient notes (numeric)	X X X
Respiratory and in-hospital complications	Patient notes		...	X	X
Hospital length of stay	Patient notes (numeric)				X		
Mortality (if applicable)	Patient notes (binary)				X	X	X
EORTC- QLQ-C30	Standard question-	X	X	X

	aire (numeric)						
DN4 pain questionnaire	Standard questionnaire (numeric)	X	X	X
Adverse events (if applicable)	Patient notes and procedure (descriptive)				X	X	X
Protocol deviations (if applicable)	Patient notes and procedure (descriptive)				X	X	X

Consent and eligibility will be evaluated by the research team. Data recording will be collected by the research nurses.

To maximise completeness of data, the research team will review the patients at the beginning of the day for expected hospital location, review patients after their surgery for data completeness, highlighting the patients at nurse handover, and posting coloured laminates for instructions of the analgesia pumps. In the period after hospital discharge, patients will receive questionnaires by post and email, and receipt and completion followed up by a phone call.

13.2 Data handling and record keeping

The data will be stored on on-site, on protected research laptops within the research department in locked rooms, with limited and restricted access. The data collected will be pseudo-anonymised, with an enrolment number allocated to the participant's data. This allocation data will be held within the research department's laptop, with security as outlined in the previous question.

14 Statistical Considerations

The research team statistician, Dr D Wong will analyse the data.

14.1 Sample size calculation (some pilot/feasibility studies may not require a formal sample size calculation)

Our unit performed 350 VAT lung cancer resections in 2016. We estimate that 50% (175) will be eligible from our study criteria, and recruitment to be 60% (105). We envisage that recruitment will take at least 12 months with a conservative estimate of 18 months, with final six-month follow-up at 24 months. From local audit data, we aim to detect a difference of at least 30% in the proportion of patient experiencing moderate-to-severe pain of NRS ≥ 3 between the study groups at the 24h time point. With a power of 80% and error of 0.05, we calculate that 42 patients per group are necessary. To allow for incomplete data, we aim to recruit 50 patients per group.

Participants will be randomised on the day of surgery to the 'pre-PVB LA' or 'pre-PVB saline' arm, by a study investigator, with a 1:1 randomisation ratio using 'Castor' online software. Each subject will receive a unique randomization code in an envelope that will only be opened during the preparation of the pre-PVB injectate. Authorised staff will be allocated a username and password for the randomisation system. Patients may only be randomised into the study by an authorised member of staff at the study site, as detailed on the delegation log. The research team member, who is responsible for randomisation (not blinded) will perform this in a separate location to the other research team members. Patients may only be randomised into the study once.

14.2 Statistical analysis

Demographic characteristics and other baseline characteristics (e.g. clinical measures taken at baseline) will be summarised by appropriate descriptive statistics according to treatment group in accordance to CONSORT guidelines (<http://www.consort-statement.org>). Patient outcomes will be analysed according to intention-to-treat.

Primary outcome:

The proportion of patients with clinically relevant moderate-to-severe pain (Numerical Rating Scale [NRS] ≥ 3) related to the surgical site at rest at 24h in treatment (pre-PVB LA) and control (pre-PVB saline) arms will be compared using the chi-square test for equality of two proportions

Secondary outcomes:

For all secondary outcomes, the distributions of outcome variables will be assessed for normality. To compare outcomes between treatment and control arms, we will use Student's t test to for normally-distributed continuous outcome variables, the Mann-Whitney test for non-normally distributed continuous and ordinal outcome variables, and chi-square tests for binary outcome variables.

There is no plan for interim analysis of the data, and the data collected up to the point of any withdrawals will be included in the final analysis.

14.3 Interim analysis and data monitoring

14.3.1 Stopping / discontinuation rules and breaking of randomisation code

Completion of the trial is completed after the follow-up period of the 100th participant has been completed. There will be no interim analysis.

The randomisation code will be broken only in the perioperative phase of the study, in the event of a serious adverse event (suspected local anaesthetic toxicity with haemodynamic instability) when the patient must be treated. All other conditions are identical after the operative theatre phase of the study.

14.3.2 Monitoring, quality control and assurance

This is a single centre trial, and data quality will be checked at the end of the trial. Good clinical practice and research governance guidelines will be adhered to at all times.

15 Ethical Considerations

The study has Sponsor approval and has been submitted to xxx REC and HRA and received appropriate approvals – REC reference x19/XX/xxxx. Consent will be gained from patients prior to their participation. Any patient facing information will be approved by REC.

Because standardised questionnaires will be used to measure outcomes, non-English speakers will be not be included in the study.

Patient and public involvement

Our research question addresses a main concern of patients undergoing surgery for cancer: postoperative pain and recovery after surgery.

1. Cancer Patient Panel Group (South East London Cancer Research Panel) on the 17th July 2015

In the design stages of our study, following our first audit, we presented and discussed our proposal and received written feedback:

Efficacy of preoperative paravertebral block analgesia in elective thoracic surgery for lung cancer resection

**Biomedical Research Centre
Guy's & St Thomas' NHS Foundation Trust and King's College London**

Feedback to researcher template

1) Using your own words where possible what do you think this research project is about?

To compare the outcomes for patients in terms of pain control and recovery times of having both a pre-operative and post-operative block analgesic injection.

2) This research project looks like a good idea to me:

Strongly disagree	<input type="checkbox"/>	Disagree	<input type="checkbox"/>	Neutral	<input type="checkbox"/>	Agree	<input type="checkbox"/>	Strongly agree	<input checked="" type="checkbox"/>
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Comments:

It is a commonly used procedure in other surgeries and appears to work. There is need to check for currently unknown risks or side effects but it would seem that the sooner it is standard procedure the better.

3) If I was eligible I would be willing to participate:

Strongly disagree	<input type="checkbox"/>	Disagree	<input type="checkbox"/>	Neutral	<input type="checkbox"/>	Agree	<input type="checkbox"/>	Strongly agree	<input checked="" type="checkbox"/>
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Comments:

4) The target group would think this research project was a good idea:

Strongly disagree	<input type="checkbox"/>	Disagree	<input type="checkbox"/>	Neutral	<input type="checkbox"/>	Agree	<input type="checkbox"/>	Strongly agree	<input checked="" type="checkbox"/>
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Comments:

5) The proposal is sensitive to the experiences and feelings of the target group:

Strongly disagree	<input type="checkbox"/>	Disagree	<input type="checkbox"/>	Neutral	<input type="checkbox"/>	Agree	<input type="checkbox"/>	Strongly disagree	<input checked="" type="checkbox"/>
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Comments:									
6) <u>There shouldn't be a problem with recruitment, or the commitment of participants:</u>									
Strongly disagree	<input type="checkbox"/>	Disagree	<input type="checkbox"/>	Neutral	<input type="checkbox"/>	Agree	<input type="checkbox"/>	Strongly agree	<input checked="" type="checkbox"/> x

Comments:									
<p><i>The advantages seem so obvious, I imagine some participants might not want to be in the control group. Though it was stated that should the benefits become overwhelming obvious, the trial would be stopped and the procedure changed, this would be too late for those in the control group who had already had their surgery.</i></p>									
7) <u>It's written in a way that would allow most people to understand the words and ideas:</u>									
Strongly disagree	<input type="checkbox"/>	Disagree	<input type="checkbox"/>	Neutral	<input type="checkbox"/>	Agree	<input type="checkbox"/>	Strongly agree	<input checked="" type="checkbox"/> x
Comments:									

8) <u>It's the right length:</u>									
Strongly disagree	<input type="checkbox"/>	Disagree	<input type="checkbox"/>	Neutral	<input type="checkbox"/>	Agree	<input type="checkbox"/>	Strongly agree	<input checked="" type="checkbox"/> x
Comment:									

9) Which aspects of the proposal work well?						
Comment:						
<p><i>I think it is a clearly explained proposal. Couple of suggestions overleaf.</i></p>						
10) What might make it better?						

Comment:

1. *It might be helpful for further clarification to add a sentence to the last para on page 1. "This study is to assess whether patients undergoing lung cancer resection would benefit for the preoperative paravertebral block treatment"*
2. *Under 'side effects' on page 2, are these risks that might apply for patients having the routine postoperative block – or are they increased if both blocks are used?*
3. *As suggested in the discussion, clarify the meaning of the first sentence under 'Risks'*

11) Any other questions or concerns that haven't already been addressed above?

Comment:

Thank you for your presentation and for answering our questions so fully.
Good luck with your application and with your work. You sound like a strong and united team.

The patient group gave us detailed feedback based on their previous hospital experiences, and confirmed that this was an important topic to study. They also gave us advice on how to improve the patient understanding of the research process, and specify that all patients would receive the standard surgical treatment without additional effort.

We amended the participant leaflet on this advice, and we devised a summary to make information more easily understood, and help with recruitment.

2. SELCRP meeting on 26th August 2016

We updated the panel by presenting our changes, and on our application for a research grant (RFPB) on the 27th May 2016. We received further feedback on our patient information leaflet from the meeting organized by Ambi Williams, Research Manager at the King's Health Partners Cancer Centre:

Two members commented that the patient information summary "was fine and no further amendments" were necessary.

One member commented:

- This document is generally extremely clear and the study is well described.
- There are just a couple of areas I think could be explained or amended:
In the title the surgery is termed "elective" and, seeing this in conjunction with lung cancer where there seems very little choice, I realise I don't know what it means and would like a definition.

- In the paragraph “What will happen to me if I take part?” the phrase in line 2 “.....whether you have PVB or not.” is contradicted by the next phrase “Both groups will receive the PVB, after being put to sleep;”
- Is there any additional risk from having an additional PVB?
- “If I were a lung cancer patient in the position of needing this surgery I believe I would be happy to be part of the trial.”

We were successful in the first round, but not the second, and the feedback was reviewed with the PPI group and Jacintha McGahon from the Clinical Research Network. The feedback was that the study was worthwhile and of patient value.

3. Theatres and Perioperative Medicine (TAP) Research Group

A research group was set up in our directorate in 2017/2018 which enabled peer review of our study with constructive feedback on design and methodology.

The trial will be presented at the TAP PPI group on 28th May 2019.

16 Financing and Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If any patients are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. Guy's and St Thomas' NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered. However, legislation now requires any GMC registered medical professional to hold a valid indemnity cover.

17 Reporting and dissemination

We will present the findings at a national or international conference meeting and aim to publish the findings in a peer reviewed journal.

We have an option with the consent form to be ticked should the participant wish to be informed of the results of the study. It will be made clear that this may be up to 3 years following the commencement of the study.

We will inform participants of the key points relating to the primary and secondary outcomes when the results become available, accompanied with an explanation in lay terms as to the meaning and implications of these results.

18 Appendices

Tables, Figures, References**Appendices**

Including (where relevant):

Patient information sheet

Patient consent form

Data collection forms and validation information

Ethics form

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Useful reading/websites

Integrated Research Application System (IRAS)
<https://www.myresearchproject.org.uk/>

Health Research Authority (HRA)
www.hra.nhs.uk

HRA Guidance for Patient Information Sheet and Informed Consent
<http://www.hra.nhs.uk/research-community/before-you-apply/participant-information-sheets-and-informed-consent/>

CONSORT statement

A set of recommendations for improving the quality of reports of parallel group randomised trials

<http://www.consort-statement.org/>

ICH Harmonised Tripartite Guidelines for Good Clinical Practice (1996)

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

Martin Bland et al, Statistical guide for research grant applications

<http://www-users.york.ac.uk/~mb55/guide/guide.htm>

Includes detailed information and definitions of many aspects required for a research protocol as well as information about randomisation software and services

Martin Bland, Directory of randomisation software and services

<http://www-users.york.ac.uk/~mb55/guide/randsery.htm>

Declaration of Helsinki

(<http://www.wma.net/en/30publications/10policies/b3/index.html>)

Appendix 1 – Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	<ul style="list-style-type: none"> -Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event 	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	<p>Contact the Sponsor and MREC Immediately</p> <p>Within 3 days</p>	<p>By phone</p> <p>Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.</p>	<p>Main REC and Sponsor</p> <p>Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.</p>
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
<u>Declaration of the conclusion or early termination of the study</u>	Chief Investigator	<p>Within 90 days (conclusion)</p> <p>Within 15 days (early termination)</p> <p><i>The end of study should be defined in the protocol</i></p>	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
<u>Summary of final Report</u>	Chief Investigator	Within one year of conclusion of the Research	<p>No Standard Format</p> <p>However, the following Information should be included:-</p> <p>Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants</p>	Main REC with a copy to be sent to the sponsor