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TITLE

A Randomised Controlled Pilot Study to investigate the effectiveness of ThOracic Epidural and Paravertebral Blockade In reducing Chronic Post-Thoracotomy Pain - TOPIC Feasibility Study Protocol

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ABSTRACT

Introduction

Open chest surgery (thoracotomy) is considered the most painful of surgical procedures. Forceful wound retraction, costochondral dislocation, posterior costovetebral ligament disruption, intercostal nerve trauma and wound movement during respiration combine to produce an acute, severe post-operative pain insult and persistent chronic pain many months after surgery is common.

Three recent systematic reviews conclude that unilateral continuous paravertebral blockade (PVB) provides analgesia at least equivalent to thoracic epidural blockade (TEB) in the post-operative period, has a lower failure rate, and symptom relief that lasted months. Crucially, PVB may reduce the development of subsequent chronic pain by intercostal nerve protection or decreased nociceptive input.

The overall aim is to determine in patients who undergo thoracotomy whether perioperative PVB results in reducing chronic post-thoracotomy pain compared to TEB. This pilot study will evaluate feasibility of a substantive trial.

Methods and analysis

TOPIC is a randomised controlled trial comparing the effectiveness of TEB and PVB in reducing chronic post-thoracotomy pain. This is a pilot study to evaluate feasibility of a substantive trial and study processes in two adult thoracic centres, Heart of England NHS Foundation Trust (HEFT) and University Hospital of South Manchester NHS Foundation Trust (UHSM).

Primary objective is to establish the number of patients randomised as a proportion of those eligible. Secondary objectives include evaluation of study processes. Analyses of feasibility and patient reported outcomes will primarily take the form of simple descriptive statistics and where appropriate, point estimates of effects sizes and associated 95% confidence intervals.

Ethics and dissemination

The study has obtained ethical approval from NHS Research Ethics Committee (REC number 14/EM/1280). Dissemination plan includes: informing patients and health professionals; engaging multi-disciplinary professionals to support a proposal of a definitive trial and submission for a full HTA application dependant on the success of the study.

Registration details

ISRCTN 45041624

Strengths of this study

- Chronic pain post thoracotomy is common and can result in significant economic and healthcare burden.
- Very little is known about whether anaesthetic and analgesic technique will prevent chronic pain.
- This randomised controlled pilot study will assess patient recruitment to a definitive study.
- Results from this study will contribute towards limited evidence towards prevention of development of chronic post thoracotomy pain.

Limitations of this study

- This pilot study will not answer the research question but will lead to well-designed definitive study.

INTRODUCTION

Background

Open chest surgery (thoracotomy) is considered the most painful of surgical procedures.[1] Forceful wound retraction, costochondral dislocation, posterior costovetebral ligament disruption, direct intercostal nerve trauma and wound movement during respiration combine to produce an acute, severe post-operative pain insult and persistent chronic pain many months after surgery is common.[1-5] Chronic post-thoracotomy pain (CPTP) is defined by the International Association for the Study of Pain, as pain that recurs or persists along a thoracotomy incision at least 2 months following the surgical procedure.[6] The aetiology of CPTP seems to be both nociceptive and neuropathic in nature. Risk factors include female gender, younger age, psychological vulnerability and intercostal nerve damage.[7 8] CPTP can be very disabling and results in a substantial economic and health care burden. About 8,500 surgical lung resections are performed annually in the UK mainly for lung cancer.[9] Our literature review suggests CPTP occurs in 43% of patients, who had no pre-existing pain problem, at 6 months after surgery. Other surveys indicate 66% of patients suffered from pain that impaired normal daily activity for at least 12 months after thoracotomy, 90% of affected patients required prescription medications for pain and anxiety whilst 30% received specialist treatments.[10] About 29% of patients with CPTP have neuropathic pain that is harder to treat than somatic pain. Of these, 43% experienced some level of disruption in their employment status, including reduced working time, unemployment or early retirement.[11 12]

Current Practice

Thoracic epidural blockade (TEB) is currently regarded as the 'gold standard' for pain relief in thoracotomy; however this dogma has recently been challenged. Recent evidence from two meta-analyses and systematic reviews comparing the analgesic efficacy and side effects of epidural versus paravertebral blockade for thoracotomy pain control concluded that although the analgesia was comparable, paravertebral blockade had a better short-term side effect profile, including urinary retention, hypotension, nausea and vomiting, and pulmonary complications.[13 14]

Despite the evidence, previous surveys of clinical practice have consistently demonstrated that thoracic epidural remained the most popular choice. A survey of Australian thoracic anaesthetists in 1997 revealed that 79% regarded TEB as the method of choice for analgesia in thoracotomy.[15] Similar results were found in the UK with 80% of anaesthetists considered TEB as the best mode of pain relief for upper abdominal surgery.[16] A 2008 survey of all 38 thoracic units in the UK that was carried out by the Association of Cardiothoracic Anaesthetists (ACTA) reported that the majority of thoracic anaesthetists (2/3 units) prefer TEB to PVB, which suggests that most thoracic anaesthetists have yet to be convinced by the evidence available.[17]

Effect of anaesthesia and analgesic technique

The physiological response to surgically induced tissue injury is analogous to an acute systemic inflammatory response. This is pertinent to thoracotomy, during which musculoskeletal disruption

from retraction, intercostals nerve injury and pleural breach is impossible to avoid even with meticulous surgical technique. It is almost certain that the interaction of these factors produce the conditions which result in the high prevalence of CPTP.[8 18 19] The somatic afferent neuronal traffic generated by surgery is integrated at spinal cord level before onward transmission to the higher central nervous system. Elaboration of this input via the thalamus and onward to the cerebral cortex results in the sensation of localised acute pain and the psychological and emotional responses of distress. This afferent information can be modulated by therapeutic nerve blockade or a reduction in its humoral consequences e.g. by the addition of anti-inflammatory agents. Nerve block reduces acute symptoms by preventing pain transmission. It may also reduce the complex "Elaboration" of pain pathways at a spinal cord level and thus desensitise pathways which underpin the development of chronic pain. Preventing this sensitisation is proposed as the basis for so called "Pre-emptive analgesia".[11] If spinal cord sensitisation does play a role in CPTP, it follows that the less excitatory information transmitted to spinal cord level, the greater the chance of chronic pain prevention. Although TEB and PVB both utilise local anaesthetics to reduce afferent input, their sites of action are different. TEB is a central neuraxial blockade, effective at spinal cord level bilaterally. It does not induce complete neural "Silence" but reduces onward transmission by a combination of local anaesthetic induced sodium channel blockade and opioid interaction in the substantial gelatinosa. By contrast, the effect of PVB is dependent on local anaesthetic mediated prevention of peripheral nociceptive afferent traffic reaching the spinal cord.[20 21] In this sense, quiescence of this neuronal input may be more complete with an effective PVB. There is therefore a sound theoretical basis to hypothesise divergent effects of the two techniques on cord sensitisation and subsequent CPTP generation.

The evidence for the comparative effectiveness of PVB and TEB

Three recent systematic reviews conclude that unilateral continuous paravertebral blockade (PVB) provides analgesia at least equivalent to TEB in the post-operative period, has a lower failure rate, and symptom relief that lasted months.[13 14] PVB resulted in fewer pulmonary complications, less urinary retention, hypotension and nausea/vomiting.[22] In 2005, in a multicentre UK audit of 365 pneumonectomies, PVB was associated with significantly lower major post-operative complications (23% vs 35%) and lower unexpected ICU admissions (8% vs 18%) compared with TEB.[23] The benefits seen with PVB can be explained by the blocking of unilateral intercostals nerves only, with preservation of respiratory and sympathetic function on the contra-lateral side. These reviews were updated in October 2012 with 6 additional trials, 5 of which[20 22-25] (total n=244) supported the conclusions of the systematic reviews, however a small trial found median morphine consumption significantly higher with PVB (n=12) than TEB group (n=12) (9 vs 36 mg, p= 0.003).[20] Crucially, PVB may reduce the development of subsequent chronic pain by intercostal nerve protection or decreased nociceptive input.[21]

Previous trials directly comparing TEB and PVB have not examined chronic pain as the primary outcome and as a result, evidence that PVB is superior in preventing CPTP is derived from other sources. PVB has long been utilised as a treatment (rather than prevention) of CPTP to good effect, with symptom relief lasting months. Observational studies have reported lower chronic pain rates after PVB relative to TEB, albeit with non-randomised methodology. Local anaesthetic induced PVB

has been proven to abolish cortical somatosensory evoked potentials from thoracic dermatome stimulation.[21] There is no evidence for an equivalent abolition in TEB. Prevention of afferent input to the central nervous system is known to be important in pain modulation. Total blockade of somatosensory evoked potentials by PVB removes the stimulus for central sensitisation and could be uniquely effective in preventing CPTP from being triggered. There are many parallels between CPTP and chronic pain after breast surgery with recent trial evidence suggesting that PVB exerts a beneficial effect in chronic pain prevention.[20 26]

The most recent Cochrane Review comparing PVB and TEB in adults undergoing thoracotomy found no difference between PVB and TEB in 30 day mortality following surgery.[27] PVB was associated with a lower incidence of pneumonia and delirium when compared with TEB. No significant difference between PVB and TEB was found in critical care admission and there was insufficient data to compare the two techniques in terms of cardiovascular complications or the need for further surgery. In terms of analgesic efficacy, PVB was comparable to TEB and was found to be superior at 24 hours post-operatively. PVB also had a better minor complication profile with lower incidence of hypotension, nausea and vomiting, pruritis and urinary retention. No difference between PVB and TEB was found in excessive sedation and length of hospital stay. There was insufficient data to compare PVB and TEB in terms of assessing chronic post-thoracotomy pain and health costs.

The review also concluded that a well-conducted randomised controlled trial comparing PVB and TEB in thoracotomy is needed. Areas that require further research include 30 day mortality, major complications, chronic pain and health costs.

Study Rationale

Chronic post-thoracotomy pain (CPTP) is unpleasant and disabling. Surveys have indicated 66% of patients suffered pain that impaired their normal daily activity for at least 12 months after thoracotomy.[10] 90% of affected patients required prescription medications for pain and anxiety. Of these, 43% experienced disruption in their employment status. CPTP certainly results in substantial economic and health care burden. It is expected that the number of patients suffering CPTP will increase following the rise in number of lung resections over the last decade (around 60%) in the UK and Ireland. There is now an urgent need to answer this important research question for benefits to patients and the NHS.

If one technique proves to be significantly better, our results will influence national policy and directly improve patient care. Our results will also be applicable to the prevention of chronic post-surgical pain from other oneside operations, such as hernia repair, leg amputation, gallbladder removal or breast surgery.

Study Aim

The overall aim of this research is to determine in adult patients who undergo open chest operation whether perioperative paravertebral blockade (PVB) at thoracotomy results in reducing chronic post-thoracotomy pain compared to thoracic epidural blockade (TEB). To answer this research

question with authoritative evidence of clinical and cost effectiveness of PVB, a multi-centre randomised controlled trial with a parallel health economic evaluation is required.

However, feasibility studies are the best way to assess feasibility of a large, expensive full-scale study, and in fact are an almost essential pre-requisite. Conducting feasibility prior to the main study can enhance the likelihood of success of the main study and potentially help to avoid doomed main studies.[28] We have therefore designed this multicentre feasibility study comparing the effectiveness of thoracic epidural blockade and paravertebral blockade in reducing chronic post-thoracotomy pain. This study will evaluate feasibility of a substantive trial and study processes by making the following qualitative and quantitative assessments.

Objectives for the feasibility study

The aims of the feasibility stage are to assess various aspects of the trial design and management and not to determine the relative effectiveness of PVB and TEB.

Primary Objective

To establish the number of patients randomised as a proportion of those eligible to enter the study.

Secondary Objectives

1. Assessment of effectiveness of patient identification and screening processes
2. Identification and analysis of any reasons for failure to recruit patients
3. Examination of the educational materials provided to surgeons and anaesthetists to ensure they are fit for purpose.
4. Assessment of willingness of surgeons and anaesthetists to participate
5. Assessment of the effectiveness of the randomisation process of patients
6. Assessment of sustainability of single-blinding of patients to treatment allocation
7. Evaluation of robustness of data collection processes during patient's hospital stay
8. The proportion of patients followed up at six months
9. Acceptability to and impact on patients of the interventions
10. Assessment of trial processes, including the choice of outcome measures and impact on staff
11. Derivation of the preliminary data from clinical outcome measures to inform the sample size calculation for the substantive study.

TRIAL DESIGN

Design

TOPIC is a randomised controlled trial comparing the effectiveness of thoracic epidural blockade and paravertebral blockade in reducing chronic post-thoracotomy pain. This is a pilot study to evaluate feasibility of a substantive trial and study processes.

Setting

The study started in July 2015 with final follow-up to end December 2016. Two adult thoracic centres, Heart of England NHS Foundation Trust (HEFT) and University Hospital of South Manchester NHS Foundation Trust (UHSM), with a patient case mix and size typical of UK thoracic anaesthetic practice, will take part in this feasibility. Based on National Thoracic Surgery Activity and Outcome Report and local audit data, an estimated total of 500 elective open thoracotomies were performed at BHH (n=400) and at UHSM (n=100) in 2011. All adult patients admitted for elective thoracotomy who fulfil the inclusion and exclusion criteria during the study period will be approached at both sites. The coordinating centre will be based within MIDRU in Birmingham Heartlands Hospital.

Flow of Participants during the trial

The anticipated journey of participants through the trial is depicted in the flow chart as indicated in Figure 1.

All adults undergoing planned elective thoracotomy at study sites fulfilling inclusion and exclusion criteria will be approached and the trial written information sheets will be given to them and the study will be discussed fully. Written Informed consent will be obtained. Patients who consent to participate in the trial will be randomised to either receiving TEB or PVB arm which will be delivered during the patient's surgery by either a Surgeon or Anaesthetist trained in the study protocol. Patient will be randomised on the morning of the surgery. If either surgeon or anaesthetist is not available to deliver the intervention, randomisation will not go ahead.

Pre and post-surgery study data collection will be performed and study questionnaires will be completed, as detailed. Adverse events will be collected throughout the duration of patients' participation in the study. Figure 2 is a summary of investigations and assessment.

Study Eligibility

Inclusion Criteria

- Aged ≥18 years
- Elective open thoracotomy
- Able to understand the study information and provide written informed consent
- American Society of Anaesthesiologists physical status I, II or III
- Not known to be pregnant

Exclusion Criteria

- Known allergy to local anaesthetics;
- Infection near the proposed puncture site;
- Coagulation disorders;
- Thoracic spine disorders
- Chest wall resection
- Emergency thoracic surgery
- Previous thoracotomy
- Likely inability to comply with completion of the study questionnaires

Patient identification and screening procedure

Research staff will work in close liaison with the multidisciplinary team responsible for routine patient care. Patients listed for elective open thoracotomy will be identified and screened for eligibility at clinics prior to their planned surgery. If a patient is screened but is not eligible for the TOPIC trial or consent for randomisation is not given, a record of the case will be kept in the screening log. The log will collect hospital number, patient's initials, date of birth, age, ethnic group, BMI and reason not eligible for the trial. The log should be kept in each study centre's site file and a copy (in an anonymised format – removing initials and hospital number) sent to TOPIC trial office. This will inform recruitment targets. No further information will be collected on ineligible patients or those that have not given consent for randomisation.

Patient recruitment

Ideally consent should be sought under unhurried circumstances when entry criteria are fulfilled. Consent is sought in several stages. We aim to identify patients who will need a planned surgical thoracic operation within the two recruiting study sites. Eligible patients will be identified in clinics prior to surgery. Ethically approved participant information sheet will be given to eligible patients, supported by face to face discussion with the research team and their consultant. The participant information sheet has been developed with feedback from our PPI representatives, and any

ambiguities, or questions frequently asked by those approached, will be collated. This will enable a comprehensive, but clear, participant information sheet to be deployed if we proceed onto a substantive trial.

If patient consents to participate in the study, written informed consent will be obtained by a member of the research team. Enough time will be given to discuss the study, ask any questions before seeking consent. If the patient decides to enter the trial, they will be asked to sign two original copies of the Patient Consent Form which will then be countersigned by the member of the research team taking the consent. The patient will retain one copy of the signed Consent Form. The second copy will be photocopied and the photocopy placed in the patient's medical records whilst the original will be retained in the Investigator Site File.

Participants will be asked to consent to their GP being informed about their participation in the study.

Randomisation

After written informed consent, the patient will be randomised, on the day of surgery, to either thoracic epidural blockade (TEB) or paravertebral blockade (PVB). Participants will be individually randomised into the study in an equal 1:1 ratio. Randomisation will be by a web based randomisation system, with a telephone option available as back-up, managed by the Birmingham Clinical Trials Unit (BCTU).

A 'minimisation' procedure using a computer-based algorithm and incorporating a random element will be used to avoid chance imbalances in the following variables. The variables chosen are:

- Gender
- Age <65 years or ≥65 years
- Centre (Birmingham Heartlands Hospital or University Hospital of South Manchester)
- Thoracotomy for lung cancer resection or for other indication

Using the web-based randomisation service, patients will be allocated to a treatment group. The anaesthetist and surgeon in charge of patient care will be informed of the patient's allocation. A unique study identification number will be assigned to the participant.

Study anaesthetic and analgesic strategies

All study patients will be anaesthetised by experienced thoracic anaesthetists (consultants) who have been trained and deemed competent in both anaesthetic techniques. The study team has worked closely with consultant anaesthetists to develop a suitable training package. Consultant anaesthetists are capable to perform both epidurals and paravertebral blocks however for the purpose of the study, anaesthetists will be asked to perform the techniques to the standard required by study protocol. Two online training videos detailing thoracic epidural and paravertebral blocks have been produced alongside supplementary written step-by-step guide. A copy of the videos is also available in DVD format. All anaesthetists participating in the study must review both video and/or written material and confirm that they are able to perform the techniques according to study

protocol. Further training, if required, will be provided by study-designated trainers at each participating sites who can demonstrate and observe performance if required. All training material will be freely available at each site and will act as a reference for participating anaesthetists and surgeons. Training by participating anaesthetists will be documented in training logs.

To be pragmatic, some variation in technical aspects of block insertion detailed in the training is anticipated, both between experienced thoracic anaesthetists, and those trained for the trial, and between centres, as anaesthetists will use their judgment on the best techniques for each patient. This represents real world variation in anaesthetic practices and will not contribute to bias since randomisation will ensure balance across groups by centre. The location and dose of anaesthetic will be captured on a post-operative case report form (CRF).

Experimental group: Paravertebral blockade

Three single injections, awake or asleep, using 16G/18 G graduated epidural needle with 15ml 0.25% bupivacaine at T3-4, 5-6 and 7-8, will be given. The PVB catheter will be placed at T5 under direct vision by a surgeon during surgery. A loading dose of 10ml 0.25% bupivacaine is given before chest closure followed by infusion of 0.125% bupivacaine 0.1-0.25ml/kg/h. See Appendix for further details.

Control group: Thoracic epidural blockade

Usual practice of TEB, awake or asleep, using 16G/18G graduated epidural needle with a catheter inserted at the spinal level supplying the skin at the incision site, a test dose of 3ml of 0.25% bupivacaine, and a loading dose of 0.25% bupivacaine 0.1ml/kg with up to 3mg of diamorphine. This will be followed by infusion of 0.125% bupivacaine with 2mcg/ml fentanyl at 0.1-0.25 ml/kg/h. See Appendix for further details.

Study Treatment Dispensing

All anaesthetics and analgesia will be taken from standard theatre pharmacy stock. As TOPIC does not fall under the Medicines for Human Use (Clinical Trials) regulations 2004, segregated stocks for trial use and specific trial labelling is not required. Temperature monitoring should follow local pharmacy practice and deviations need not be reported to the TOPIC Study Co-ordinator.

Blinding of trial allocations

By the nature of the interventions it is not possible to conceal treatment assignments from surgeons and anaesthetists. Moreover, from a safety aspect, it is vital that the nursing staff caring for the patient know the amount of epidural opiates prescribed before administering systemic opiates, and known adverse events such as hypotension or pruritis expected to arise from the respective anaesthetic approaches.

Every attempt will be made to blind study participants to their group allocation. The epidural or paravertebral block infusion catheter will be taped laterally on the side of operation so no visible difference can be seen by the patient. Infusion pumps used by both groups will also be identical.

Withdrawal from the Trial

Withdrawal from the trial before surgery is a decision of the participant, however, withdrawn patients can bias trial results and reduce the power of the trial to detect important differences, so randomisation will take place as close to the time of surgery as is practical in order to reduce post randomisation withdrawals. Following surgery participants should be encouraged to allow clinical data collection to continue even if they decline to complete further questionnaires.

Cessation of the allocated anaesthetic strategy will also be necessitated in cases where a known serious adverse reaction to the anaesthetic occurs or a suspected unexpected serious adverse reaction occurs.

Protocol Violations

Any incidences of study participants not receiving the anaesthetic strategy allocation by randomisation will be recorded. All study and protocol violations and deviations will be documented in the patients CRF and reported to the Study Sponsor via the Trial Office. Patients will be analysed according to group allocation, by intent-to-treat analysis.

Additional intraoperative analgesia

Supplementary intraoperative analgesia will not be restricted and can follow local policy. Analgesia and doses will be recorded as part of the study in the patients CRF.

Post-operative analgesia

Both groups should continue with TEB/PVB infusion of 0.1-0.25 ml/kg/h bupivacaine, in the first instance for 48 hours post-operatively. All participants will receive regular paracetamol and prophylactic anti-emetics unless contraindicated. Non-steroidal-anti-inflammatory drugs can also be administered if appropriate. All analgesic requirements will be recorded during inpatient follow-up.

For TEB group, intravenous morphine boluses will be prescribed for break-through pain which is not relieved by the epidural top ups. If the epidural is ineffective and no block is evident, the TEB can be reinserted at the discretion of the anaesthetic team. If pain relief is inadequate, morphine PCA (Patient Controlled Analgesia) can be administered.

For PVB group, intravenous morphine boluses followed by morphine PCA will commence on recovery from anaesthesia.

OUTCOMES AND DATA COLLECTION

Patient Recruitment into study

The overall aims of the feasibility are to find out if a larger trial is feasible. The quantitative measurements related to this include

- Proportion of all elective thoracic procedures screened
- Proportion of eligible participants of those screened
- Proportion of eligible participants randomised

In this feasibility study of 2-centres, Heart of England NHS Foundation Trust and University of south Manchester NHS Foundation Trust, there would be an approximate total of 500 elective open thoracotomies over the study period. The plan will be to recruit and randomise as many patients as possible over the 12 month study period. It is expected that between 50 and 75 eligible patients will be recruited from two sites.

Patient identification and screening

We would expect a very high proportion of patients to be screened across both study sites, given that only patients with planned thoracotomy will be included. The proportion of patients screened for eligibility and recorded on a screening log will be assessed and reported as proportion of patients screened from the total number of planned thoracotomies during the study period.

Reasons for failure to recruit

The proportion of patients that were missed, which should be minimal and proportion of patients who decline to take part will be recorded. Patients decline for many reasons, which should be captured whenever possible. We will consent declining patients to a short interview. The reasons for declining will be recorded anonymously and analysed by the research team. If there is a strong patient preference, the substantive trial may not be feasible, similarly if this population is disinterested or conversely, taking part in other trials that preclude concurrent participation.

Educational Materials and Training of surgeons and anaesthetists

Feedback on the appropriateness, value and acceptability of the training will be elicited from the feasibility sites, to enable refinement of the training programme for the substantive study, and to define a minimum competence. The training material will be evaluated for its ease of use should it be used in the substantive study.

Evaluation of willingness of anaesthetists and surgeons to participate

As part of preparation of the study site, all anaesthetists and surgeons in both sites will be approached to evaluate willingness to participate in the trial. The Site PI(s) and the Trial Coordinator will discuss the protocol to ensure that all inclusion/exclusion criteria and technical aspects are well

understood by the participating anaesthetists and surgeons. Patient "vignettes", both typical and unusual, will be presented during this training to establish whether uncertainty exists and therefore randomisation is ethical in all situations, or whether there are somewhere either technique is preferred. Training material will be revised, as per the feedback for use in the substantive study, portraying best practice in approaching and consenting participants.

The study team will also conduct a repeat national survey to assess willingness from the clinical community nationally towards the end of feasibility study.

Effectiveness of Randomisation process

This would be ascertained by the speed in which patients can be randomised and whether important prognostic data can be collected pre-operatively.

Assessment of Data collection process

Assessment and identification will be made for loss of data during in hospital stay to improve data collection process for the substantive trial.

Assessment of sustainability of single blinding of patients to treatment allocation

By the nature of the interventions it is not possible to conceal treatment assignments from surgeons and anaesthetists. Every attempt will be made to blind study participants to their group allocation and various methods may be considered. The patient reported outcomes will be collected remote in time from the acute intervention. There is no reason to suspect that recipients of the randomised intervention have strong pre-conceptions with regard to the relative effectiveness of each analgesic technique. In this feasibility study patients will be asked at 3 and 6 months after surgery via questionnaire which technique they think they received to test if our various methods for patient blinding were effective.

Assessment of follow-up rates

The primary outcome of the substantive study is chronic pain assessed at 6-month post-randomisation. It is therefore vital for the appropriate measures to be in place to minimize the loss of follow-up.

The research team will demonstrate and assist the patient to complete the questionnaires in person when the baseline data is collected. This face-to-face assistance and support in filling the questionnaire will help encourage patients and increase their confidence in completing questionnaires after discharge.

The patient has consented to be contacted by post or by telephone for follow-up purposes. Prior to the follow-up questionnaires being sent to patients at home, their vital status will be confirmed by a research team member from study sites. The contact information and patient status will be faxed

from study sites to BCTU for follow up purposes. Follow up questionnaire will include pain questionnaires, patient satisfaction questionnaire and assessment of single blinding. To be viable as a primary outcome, we would expect to achieve a response rate of 80% of expected patients, using various methods of contact. We should be able to capture 100% of mortality data via NHS tracing services. A withdrawal from follow-up of over 10% would be disappointing. The reasons for loss of follow-up if any will be documented and reported at the end of the feasibility study.

Patient reported outcomes

At baseline and prior to surgery, 5 sets of questionnaires will be completed. These comprise: Visual Analogue Scale score, Brief Pain Inventory interference score (BPI)[29 30], Neuropathic Pain Scale (NPS)[31], Generic health related quality of life (EQ-5D-5L)[32] and Hospital Anxiety and Depression Scale (HADS)[33].

In hospital data collection will include Visual Analogue Scale scores, Brief Pain Inventory, analgesic use, any acute complications conducted on Day 1, Day 2 and Day 3 post-surgery. Using day of surgery as Day 0, Day 1 is defined as the first full calendar day (from 12 midnight) post surgery, Day 2 is second full calendar day, Day 3 is third full calendar day.

On hospital discharge take home analgesia (TTOs), in-hospital mortality, acute complications, unplanned admission to level 2 or level 3 care including organ support and length of level2/level 3 stay, and total length of hospital stay. Assessment and identification will be made for loss of data during in hospital stay to improve data collection process for the substantive trial.

Six sets of questionnaires will be completed prior on hospital discharge and at three and six months post-randomisation: The national registry will be checked to confirm patients status prior to follow up questionnaires being sent at three and six months. These questionnaires are Patient satisfaction questionnaire with their overall care and with their pain relief and question to assess whether patient was aware of treatment allocation, Visual Analogue scale scores, Brief Pain Inventory interference score (BPI)[29 30], Neuropathic Pain Scale (NPS)[31], Generic health related quality of life (EQ-5D-5L)[32] and Hospital Anxiety and Depression Scale (HADS).[33]

Acceptability to and impact on patients

Patient interviews will explore the acceptability of the intervention to patients and any impacts on their stay in hospital and post-discharge. Semi-structured qualitative interviews will be undertaken with up to 30 study patients with representation of patients taking part across the two sites. The interviews will be conducted at 6-8 weeks post-discharge. This will allow for a reasonable recovery period post-surgery and will enable interviews to be undertaken with the small proportion of patients who go on to need chemotherapy, prior to this treatment beginning. The interviews will be done by telephone in order to minimise the disruption to and effort required by patients.

All patients will be eligible for interview and will be selected using maximum variety sampling by age, sex and ethnic group.[34] The need for a maximum variety sample will be balanced against spacing the interviews as evenly as possible across the 12 months of the trial so that any variations in how

the trial is implemented are reflected in the patient sample. Interviews will be conducted until saturation is achieved, which is likely to be around 30 patients.[35]

A framework for the patient interviews will be developed in months 1-3 of the trial set-up period, with reference to the literature on similar trials. The framework will also be discussed with Clinical Research Ambassador Group (CRAG) based within Heart of England NHS Foundation Trust. It will include 5 core questions that will be asked of all patients, which will cover;

- reasons for taking part in the trial
- assessing whether patients knew which anaesthetic strategy they received
- the effectiveness of staff and written communication about the trial
- how the trial impacted on their stay in hospital and at home following discharge
- suggestions for making improvements to the recruitment processes

The semi-structured nature of the interviews will allow patients to raise issues which may not have been anticipated by the research team, and will allow the interviewer to explore any patient concerns in depth. The interviews are expected to last an average of 15-20 minutes, and will be recorded digitally. If during the interviews, any patients indicate that they have unresolved concerns or clinical symptoms, they will be directed to their named research nurse. Similarly, if patients get upset the interviewer will ask for the patient's consent to be contacted by their dedicated research nurse for further discussion.

Telephone interviews will also be undertaken with up to 10 patients who declined to take part in the trial, to explore their reasons for declining and to identify how a larger trial could be adapted to encourage higher rates of participation.

Assessment of trial processes and impact on staff

Semi-structured qualitative interviews with clinical and research staff will be undertaken to explore the effectiveness and efficiency of the trial processes. This will include exploring a number of the secondary outcomes:

- the effectiveness of the patient identification and screening processes
- identification of reasons for failure to recruit patients
- the willingness of surgeons and anaesthetists to take part
- the effectiveness of the randomisation process.

Interviews will also ask for staff ideas for improvement in trial processes, and explore whether there are any unintended consequences of the trial procedure which might have an impact on patient care processes or the organisation and management of care.

Up to 20 staff interviews will be undertaken, which will be spread evenly across the two sites and will include the main clinical and managerial roles affected by the trail. The interviews will be undertaken in the month following the discharge of the last trial patient home. The interviews are expected to last an average of 20-30 minutes, and will be recorded digitallyData Collection and Management

All data for an individual patient will be collected by each Principal Investigator or their delegated nominees and recorded in the study specific data collection forms (CRF). Participants will only be identified through their unique Trial Number allocated at the time of randomisation and their initials. Data will be collected from the time the patient is entered into the trial through their discharge from hospital and up to 6 months post-surgery.

STATISTICS AND DATA ANALYSIS

Sample size calculation

We expect to recruit between 50 and 75 patients depending on the number we find eligible for the study. For example, we estimate that there will be approximately 500 open elective thoracotomies over 12 months from the two sites (Heart of England NHS Foundation Trust and University Hospital of South Manchester NHS Foundation Trust), of which 60% will be eligible, (300). Using our own target criteria of 25% recruited would make 75 participants. This number will allow us to measure the recruitment rate with 95% confidence interval (CI) of width approximately 10%. It will also be enough to estimate the standard deviation (SD) of VAS score with 95% CI of width 7 points (assuming the SD is around 25 points).

Data Analysis

The size of this study will not allow reliable assessment of the effect of the intervention on outcomes and so hypothesis testing is not proposed. Analyses of feasibility and patient reported outcomes will primarily take the form of simple descriptive statistics (e.g. proportions & interquartile ranges, means and standard deviations) and where appropriate, point estimates of effects sizes (e.g. mean differences and relative risks) and associated 95% confidence intervals.

In the first instance, for patient reported outcomes, participants will be kept in the groups they were allocated, regardless of compliance with treatment (intention-to-treat). Analysis will be completed once all patients have completed six month follow-up. A Statistical Analysis Plan will be generated for review by the Trial Oversight Committee before any analysis takes place.

Handling Missing Data

There is a potential for some missing data to occur at follow-up, however, a member of the research team will contact patients for any missing data (for example questionnaire) via telephone and post. Where patients attend for follow-up clinic, the potential for missing data will again be limited, and the secondary outcome data will also be collected at this point. Imputation of missing responses is not proposed for patient reported outcome as this is not a definitive trial and no hypothesis testing will be performed

Data Management and Quality Assurance

Data management and confidentiality

Personal data and sensitive information required for the TOPIC feasibility study will be collected directly from trial participants and hospital notes on data collection forms, coded with the participant's unique trial number and initials. All other patient identifiable information will be removed. Participants will be asked for their consent to transfer this information, including their

name and contact address for follow up to the BCTU office based in University of Birmingham. The data collected will be entered onto a secure computer database by BCTU staff. This database, once completed will be locked under the direction of Lee Middleton (Senior Statistician) for analysis.

All personal information received in paper format for the trial will be held securely and treated as strictly confidential according to NHS policies. All staff involved in the study (clinical, academic, BCTU) share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be stored on a secure server at Birmingham Clinical Trials Unit (BCTU) under the provisions of the Data Protection Act and/or applicable laws and regulations. The trial coordinator, study statistician and the data manager will have access to the database until completion of the analysis. Data may be accessed by external regulatory agencies and the Study Sponsor representatives and permission for this access will be documented within the participants consent form.

Data Quality Assurance and Validation

The study will adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the study data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry of paper questionnaires will be periodically undertaken on small sub-samples. The trial statistician (Lee Middleton) will regularly check the balance of allocations by the stratification variables. Source data verification will only be employed if there is reason to believe data quality has been compromised, and then only in a sub-set of practices.

Quality assurance will begin with a clearly documented staff training programme. A register of staff who have been trained, and their competence assessed will be maintained, and only staff whose names appear on this list will be permitted to undertake study procedures. Staff will also receive regular update training and periodic reassessment of their competence. Real-time reports will be available to staff indicating missing test and questionnaire data for all participants at that centre. This will be supplemented by regular reminders from the TOPIC Trial Office for incomplete data.

Monitoring and Audit

The study will be monitored and/or audited by Heart of England NHS Foundation Trust under their remit as Sponsor and other regulatory bodies to ensure adherence to Good Clinical Practice and the NHS Research Governance Framework for Health and Social Care (2nd edition).

Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Co-ordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of study data as an on-going activity.

The first study participant who has been randomised, received surgery and completed up to the 72 hour follow up stage of the protocol will be monitored by the Sponsors QA Manager to ensure the protocol is fit for purpose and review protocol adherence. Monitoring of study participants by the

Sponsors QA manager will then occur at random intervals throughout the study based on recruitment.

Study conduct will be subject to systems audit of the Study Record for inclusion of essential documents; permissions to conduct the trial; Study Delegation Log; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs. This will be led by the Trial co-ordinator and reported back to the Sponsor and the Sponsorship Oversight Committee.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10%) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the study database will be checked. Where corrections are required these will carry a full audit trail and justification.

Study data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

Long-term storage of data

Trial data will be stored archived after the formal closure of the trial in accordance with archive policy and for the appropriate duration as per current legislation.

The Computer database may be stored within the BCTU and will be processed according to their trial archiving policies.

SPONSORSHIP AND INDEMNITY

Heart of England NHS Foundation Trust will act as the Sponsor to this study. Delegated responsibilities will be assigned to the Chief Investigator and the NHS Trust(s) taking part in this study. The non-commercial model clinical trials agreement will be used with all participating sites detailing their local responsibilities.

Heart of England NHS Foundation Trust holds standard NHS Hospital indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

REGULATORY APPROVALS

The study has obtained ethical approval from NHS Research Ethics Committee (REC number 14/EM/1280).

FUNDING

This work was supported by National Institute for Health Research for Patient Benefit Programme grant number (PB-PG-0213-30126).

STUDY DISSEMINATION

This feasibility study is designed to identify if a substantive trial is possible. Although a definitive answer to the key research question on effectiveness of paravertebral blockade on CPTP cannot be provided, the findings of this feasibility study will be of scientific interest to others in their own right. The feasibility study will be registered on clinical trials database (www.clinicaltrials.gov). We plan the dissemination strategy in three aspects. The first will ensure that patients and health professionals are informed of the feasibility findings; the second will engage multi-disciplinary professionals to support a proposal of a definitive RCT and the third will be to resubmit for a full HTA application dependant on the success of the feasibility study.

AUTHORS' CONTRIBUTIONS

We can confirm that all authors have made substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data. JY and TM drafted the manuscript. AK, BN, LM, KT, JD and FG revised it critically for important intellectual content. All authors approved final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING STATEMENT

This work was supported by National Institute for Health Research for Patient Benefit Programme grant number (PB-PG-0213-30126).

COMPETING INTERESTS STATEMENT.

The authors declare no conflict of interest.

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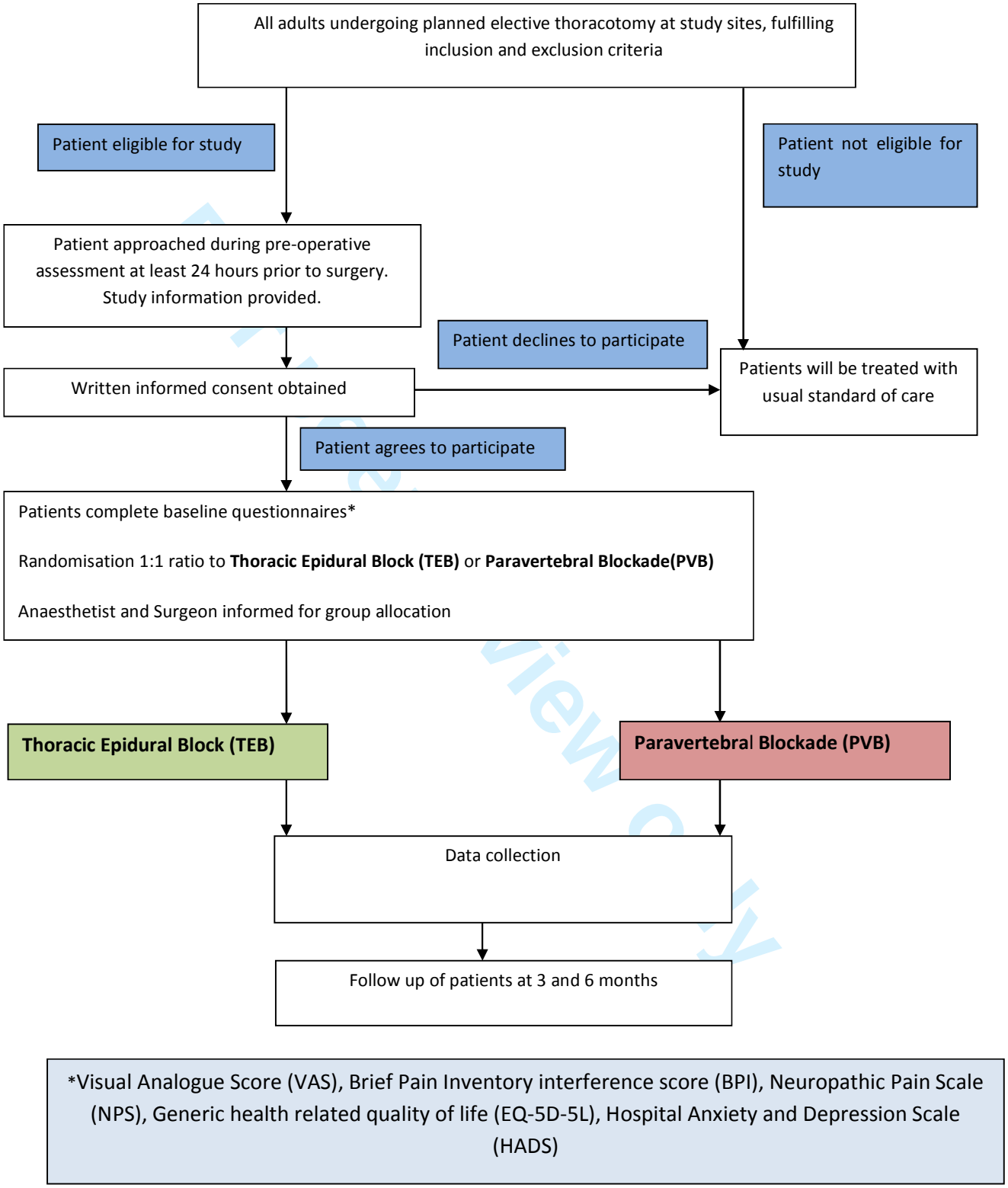
LEGENDS

Figure 1 Flow of Participants during the Trial

Figure 2 Summary of investigations and Assessments

Day one is first full calendar (from 12 midnight) post surgery, Day two is second full calendar day, Day three is third full calendar day.

Figure 1 Flow of Participants during the Trial



	Baseline	**In-hospital**				**Follow-up**		
	Clinic appointment prior to surgery	Intra-operative	Day one*	Day two*	Day three*	Hospital discharge	Three months	Six months
Eligibility and written informed consent[1]	X							
Demographic data	X							
Previous Medical History	X							
Randomisation	X **Day of surgery**							
TEB/PVB insertion data		X						
Other intraoperative data		X						
Post operative observations			X	X	X	X		
Post-operative pulmonary complications			X	X	X	X		
Visual Analogue Scale score	X		X	X	X	X	X	X
Brief Pain Inventory	X		X	X	X	X	X	X
Post-operative analgesic use			X	X	X	X	X	X
Acute Complications			X	X	X	X		
Hospital Length of Stay						X		
Mortality						If applicable		
Neuropathic Pain Scale	X					X	X	X
Discharge data and histology data						X		
EQ-5D-5L	X					X	X	X
Hospital Anxiety Depression Scale	X					X	X	X
Patient satisfaction						X	X	X
Adverse Events	If applicable							
Protocol deviations	If applicable							

APPENDIX

Thoracic Epidural Blockade Template

General points on Insertion of TEB Catheter

- Institute full monitoring according to AAGBI guidelines.
- TEB can be inserted in patients awake or asleep, sitting or in lateral position
- Catheter insertion should be at mid thoracic level (T6-T7 or T7-T8)

Intra operative Utilisation of TEB catheter

- First dose is given with 3-5 ml of 0.25% bupivacaine with 2-3 mgs of diamorphine. 2mg for patients <50kg, 2.5mg for patients 50-65kg, 3mg for patients >65kg. Dose of diamorphine should be titrated if patient is more than 75 years of age.
- This mixture provides adequate analgesia for the initial skin incision and further boluses of local anaesthetics are only given if patient's physiological parameters warrants.
- Towards the end of the operation, we start our epidural infusion of 0.125% bupivacaine and 4mcg/ml fentanyl at a rate 0.1-0.25 ml/kg/h.
- All patients receive intravenous Paracetamol and NSAIDs if there are no contraindications.

Post operative Utilisation of TEB catheter

- The patient is assessed in recovery and if they have pain, further titrated boluses of 3-5mls of epidural mixture (0.125% bupivacaine with 4mcg/ml fentanyl) is given for break through pain. Bolus can be repeated.
- All thoracotomy patients are looked after in a thoracic surgical HDU. The acute pain team reviews the patients regularly and the epidural is stepped down to oral/IV analgesics after 48 hours.
- Patients are prescribed regular oral analgesics such as paracetamol and NSAIDS.
- Nursing staff regularly assesses the block height and epidural rate is titrated as per the local pain protocol.
- If the blood pressure is persistently low and other surgical causes of low blood pressure have been ruled out, the diagnosis of epidural associated hypotension is made. Metaraminol infusion is then started at 0.5-1.5 micrograms/kg body wt min^{-1} (Appendix). This avoids the need for CVC line perioperatively and restricts the amount of fluid administered.

- The pain scores at rest and when mobile, motor block, postoperative nausea and vomiting and sedation scores are also assessed regularly and recorded.

- During the post operative period any complications of epidural analgesia are noted by surgical nursing staff. Advice from the acute pain team and the anaesthetist should be sought if pain control is problematic.

- In the event when epidural is deemed ineffective, morphine boluses including morphine PCA should be prescribed.

Paravertebral Blockade Template

General points on PVB and catheter insertion

- Institute full monitoring according to AAGBI guidelines.
- PVB can be performed on patients awake or asleep, sitting or in lateral position (we prefer lateral position, asleep)
- 3 preoperative PVB injection using landmark technique at the level of T4-5, T7-8, T9-10 followed by surgical catheter insertion after the thoracotomy

Intra operative Utilisation of PVB

- 15 ml 0.25% bupivacaine with or without adrenaline (1:200000-400000) to be used for each preincisional block using landmark technique ("predetermined distance technique")
- This concentration and volume should provide adequate spread and analgesia for the initial skin incision on an patient under light general anaesthesia, who is otherwise able to tolerate one lung anaesthesia.
- We do not assume that the surgical analgesia provided by the local injections lasts longer than 2-4 hours, therefore the surgical paravertebral/epipleural catheter insertion should be performed after the thoracotomy in order to make continuous infusion possible. Within 2 hours, 10 ml 0.25% bupivacaine bolus to be administered via the catheter followed by 0.25% bupivacaine infusion with 10 ml/hour until the end of the operation.
- All patients receive intravenous Paracetamol and/or NSAIDs if there are no contraindications. The paravertebral group should have 1mg/ml morphine PCA infusion with 5 minutes lockout time for rescue pain-relief.

Post operative Utilisation of TEB catheter

- The patient is assessed in recovery and if they have pain the rate of the infusion can be changed in order to provide adequate pain-relief (0-15 ml/hour, depending on the patients' bodyweight: max. 2 mg/kg/4hour bupivacaine dose). In case of the need of higher dose 5 ml bolus should be administered first.
- All thoracotomy patients are looked after in a thoracic surgical HDU. The acute pain team reviews the patients regularly and the epipleural/paravertebral is stepped down to oral/IV analgesics after 48 hours.
- Patients are prescribed regular oral analgesics such as paracetamol and/or NSAIDS; iv morphine PCA should be available for rescue pain-relief (see above).

- Nursing staff regularly assess the pain score, neurological status, physiological parameters and the area of the anaesthetized chest wall. If the anaesthetized area unnecessarily large the infusion rate should be decreased by 2 ml/hours. The lowest rate should not be lower than 5 ml/hours. If the pain-relief is inadequate 5 ml bolus 0.25% bupivacaine should be administered and the rate should be increased back to the last adequate rate and continue with this rate till the catheter removal.

- If the blood pressure is persistently low or there any other sign of epidural spread or local anaesthetic toxicity the infusion to be stopped immediately and the patient should be managed according to the guidelines. These events will exclude the particular patient from the study.

- The pain scores at rest and when mobile, motor block, postoperative nausea and vomiting and sedation scores are also assessed regularly and recorded.

- During the post operative period any complications of epipleural/paravertebral infusion are noted by nursing staff. Advice from the acute pain team and the anaesthetist should be sought if pain control if problematic.

- In the event when epipleural/paravertebral infusion is deemed ineffective, morphine boluses including morphine PCA should be prescribed.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12, 15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18, 20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A Randomised Controlled Pilot Study to investigate the effectiveness of ThOracic Epidural and Paravertebral Blockade In reducing Chronic Post-Thoracotomy Pain - TOPIC Feasibility Study Protocol

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TITLE

A Randomised Controlled Pilot Study to investigate the effectiveness of ThOracic Epidural and Paravertebral Blockade In reducing Chronic Post-Thoracotomy Pain - TOPIC Feasibility Study Protocol

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ABSTRACT

Introduction

Open chest surgery (thoracotomy) is considered the most painful of surgical procedures. Forceful wound retraction, costochondral dislocation, posterior costovertebral ligament disruption, intercostal nerve trauma and wound movement during respiration combine to produce an acute, severe post-operative pain insult and persistent chronic pain many months after surgery is common.

Three recent systematic reviews conclude that unilateral continuous paravertebral blockade (PVB) provides analgesia at least equivalent to thoracic epidural blockade (TEB) in the post-operative period, has a lower failure rate, and symptom relief that lasted months. Crucially, PVB may reduce the development of subsequent chronic pain by intercostal nerve protection or decreased nociceptive input.

The overall aim is to determine in patients who undergo thoracotomy whether perioperative PVB results in reducing chronic post-thoracotomy pain compared to TEB. This pilot study will evaluate feasibility of a substantive trial.

Methods and analysis

TOPIC is a randomised controlled trial comparing the effectiveness of TEB and PVB in reducing chronic post-thoracotomy pain. This is a pilot study to evaluate feasibility of a substantive trial and study processes in two adult thoracic centres, Heart of England NHS Foundation Trust (HEFT) and University Hospital of South Manchester NHS Foundation Trust (UHSM).

Primary objective is to establish the number of patients randomised as a proportion of those eligible. Secondary objectives include evaluation of study processes. Analyses of feasibility and patient reported outcomes will primarily take the form of simple descriptive statistics and where appropriate, point estimates of effects sizes and associated 95% confidence intervals.

Ethics and dissemination

The study has obtained ethical approval from NHS Research Ethics Committee (REC number 14/EM/1280). Dissemination plan includes: informing patients and health professionals; engaging multi-disciplinary professionals to support a proposal of a definitive trial and submission for a full HTA application dependant on the success of the study.

Registration details

ISRCTN 45041624

Strengths of this study

- Chronic pain post thoracotomy is common and can result in significant economic and healthcare burden.
- Very little is known about whether anaesthetic and analgesic technique will prevent chronic pain.
- This randomised controlled pilot study will assess patient recruitment to a definitive study.
- Results from this study will contribute towards limited evidence towards prevention of development of chronic post thoracotomy pain.

Limitations of this study

- This pilot study will not answer the research question but will lead to well-designed definitive study
- To maintain patient safety and clinical care, post-operative clinical teams looking after patients are not blinded to anaesthetic technique patient has received. The low risk of patients knowing their treatment allocation can potentially introduce bias. To limit bias, the outcome assessors are blinded to anaesthetic techiques and patients were not informed of treatment allocation.

INTRODUCTION

Background

Open chest surgery (thoracotomy) is considered the most painful of surgical procedures.[1] Forceful wound retraction, costochondral dislocation, posterior costovetebral ligament disruption, direct intercostal nerve trauma and wound movement during respiration combine to produce an acute, severe post-operative pain insult and persistent chronic pain many months after surgery is common.[1-5] Chronic post-thoracotomy pain (CPTP) is defined by the International Association for the Study of Pain, as pain that recurs or persists along a thoracotomy incision at least 2 months following the surgical procedure.[6] The aetiology of CPTP seems to be both nociceptive and neuropathic in nature. Risk factors include female gender, younger age, psychological vulnerability and intercostal nerve damage.[7 8] CPTP can be very disabling and results in a substantial economic and health care burden. About 8,500 surgical lung resections are performed annually in the UK mainly for lung cancer.[9] Our literature review suggests CPTP occurs in 43% of patients, who had no pre-existing pain problem, at 6 months after surgery. Other surveys indicate 66% of patients suffered from pain that impaired normal daily activity for at least 12 months after thoracotomy, 90% of affected patients required prescription medications for pain and anxiety whilst 30% received specialist treatments.[10] About 29% of patients with CPTP have neuropathic pain that is harder to treat than somatic pain. Of these, 43% experienced some level of disruption in their employment status, including reduced working time, unemployment or early retirement.[11 12]

Current Practice

Thoracic epidural blockade (TEB) is currently regarded as the 'gold standard' for pain relief in thoracotomy; however this dogma has recently been challenged. Recent evidence from two meta-analyses and systematic reviews comparing the analgesic efficacy and side effects of epidural versus paravertebral blockade for thoracotomy pain control concluded that although the analgesia was comparable, paravertebral blockade had a better short-term side effect profile, including urinary retention, hypotension, nausea and vomiting, and pulmonary complications.[13 14]

Despite the evidence, previous surveys of clinical practice have consistently demonstrated that thoracic epidural remained the most popular choice. A survey of Australian thoracic anaesthetists in 1997 revealed that 79% regarded TEB as the method of choice for analgesia in thoracotomy.[15] Similar results were found in the UK with 80% of anaesthetists considered TEB as the best mode of pain relief for upper abdominal surgery.[16] A 2008 survey of all 38 thoracic units in the UK that was carried out by the Association of Cardiothoracic Anaesthetists (ACTA) reported that the majority of thoracic anaesthetists (2/3 units) prefer TEB to PVB, which suggests that most thoracic anaesthetists have yet to be convinced by the evidence available.[17]

Effect of anaesthesia and analgesic technique

The physiological response to surgically induced tissue injury is analogous to an acute systemic inflammatory response. This is pertinent to thoracotomy, during which musculoskeletal disruption from retraction, intercostal nerve injury and pleural breach is impossible to avoid even with

meticulous surgical technique. It is almost certain that the interaction of these factors result in the high prevalence of CPTP.[8 18 19] The somatic afferent neuronal traffic generated by surgery is integrated at spinal cord level before onward transmission to the higher central nervous system. Elaboration of this input via the thalamus and onward to the cerebral cortex results in the sensation of localised acute pain and the psychological and emotional responses of distress. This afferent information can be modulated by therapeutic nerve blockade or a reduction in its humoral consequences e.g. by the addition of anti-inflammatory agents. Nerve block reduces acute symptoms by preventing pain transmission. It may also reduce the complex "elaboration" of pain pathways at a spinal cord level and thus desensitise pathways that underpin the development of chronic pain. Preventing this sensitisation is proposed as the basis for so called "Pre-emptive analgesia".[11] If spinal cord sensitisation does play a role in CPTP, it follows that the less excitatory information transmitted to spinal cord level, the greater the chance of chronic pain prevention. Although TEB and PVB both utilise local anaesthetics to reduce afferent input, their sites of action are different. TEB is a central neuraxial blockade, effective at spinal cord level bilaterally. It does not induce complete neural "Silence" but reduces onward transmission by a combination of local anaesthetic induced sodium channel blockade and opioid interaction in the substantial gelatinosa. By contrast, the effect of PVB is dependent on local anaesthetic mediated prevention of peripheral nociceptive afferent traffic reaching the spinal cord.[20 21] In this sense, quiescence of this neuronal input may be more complete with an effective PVB. There is therefore a sound theoretical basis to hypothesise divergent effects of the two techniques on cord sensitisation and subsequent CPTP generation.

The evidence for the comparative effectiveness of PVB and TEB

Three recent systematic reviews conclude that unilateral continuous paravertebral blockade (PVB) provides analgesia at least equivalent to TEB in the post-operative period, has a lower failure rate, and symptom relief that lasted months.[13 14] PVB resulted in fewer pulmonary complications, less urinary retention, hypotension and nausea/vomiting.[22] In 2005, in a multicentre UK audit of 365 pneumonectomies, PVB was associated with significantly lower major post-operative complications (23% vs 35%) and lower unexpected ICU admissions (8% vs 18%) compared with TEB.[23] The benefits seen with PVB can be explained by the blocking of unilateral intercostals nerves only, with preservation of respiratory and sympathetic function on the contra-lateral side. These reviews were updated in October 2012 with 6 additional trials, 5 of which[20 22-25] (total n=244) supported the conclusions of the systematic reviews, however a small trial found median morphine consumption significantly higher with PVB (n=12) than TEB group (n=12) (9 vs 36 mg, p= 0.003).[20] Crucially, PVB may reduce the development of subsequent chronic pain by intercostal nerve protection or decreased nociceptive input.[21]

Previous trials directly comparing TEB and PVB have not examined chronic pain as the primary outcome and as a result, evidence that PVB is superior in preventing CPTP is derived from other sources. PVB has long been utilised as a treatment (rather than prevention) of CPTP to good effect, with symptom relief lasting months. Observational studies have reported lower chronic pain rates after PVB relative to TEB, albeit with non-randomised methodology. Local anaesthetic induced PVB has been proven to abolish cortical somatosensory evoked potentials from thoracic dermatome

stimulation.[21] There is no evidence for an equivalent abolition in TEB. Prevention of afferent input to the central nervous system is known to be important in pain modulation. Total blockade of somatosensory evoked potentials by PVB removes the stimulus for central sensitisation and could be uniquely effective in preventing CPTP from being triggered. There are many parallels between CPTP and chronic pain after breast surgery with recent trial evidence suggesting that PVB exerts a beneficial effect in chronic pain prevention.[20 26]

The most recent Cochrane Review comparing PVB and TEB in adults undergoing thoracotomy found no difference between PVB and TEB in 30 day mortality following surgery.[27] PVB was associated with a lower incidence of pneumonia and delirium when compared with TEB. No significant difference between PVB and TEB was found in critical care admission and there was insufficient data to compare the two techniques in terms of cardiovascular complications or the need for further surgery. In terms of analgesic efficacy, PVB was comparable to TEB and was found to be superior at 24 hours post-operatively. PVB also had a better minor complication profile with lower incidence of hypotension, nausea and vomiting, pruritis and urinary retention. No difference between PVB and TEB was found in excessive sedation and length of hospital stay. There was insufficient data to compare PVB and TEB in terms of assessing chronic post-thoracotomy pain and health costs.

The review also concluded that a well-conducted randomised controlled trial comparing PVB and TEB in thoracotomy is needed. Areas that require further research include 30-day mortality, major complications, chronic pain and health costs.

Study Rationale

Chronic post-thoracotomy pain (CPTP) is unpleasant and disabling. Surveys have indicated 66% of patients suffered pain that impaired their normal daily activity for at least 12 months after thoracotomy.[10] 90% of affected patients required prescription medications for pain and anxiety. Of these, 43% experienced disruption in their employment status. CPTP certainly results in substantial economic and health care burden. It is expected that the number of patients suffering CPTP will increase following the rise in number of lung resections over the last decade (around 60%) in the UK and Ireland. There is now an urgent need to answer this important research question for benefits to patients and the NHS.

If one technique proves to be significantly better, our results will influence national policy and directly improve patient care. Our results will also be applicable to the prevention of chronic post-surgical pain from other one side operations, such as hernia repair, leg amputation, gallbladder removal or breast surgery.

Study Aim

The overall aim of this research is to determine in adult patients who undergo open chest operation whether perioperative paravertebral blockade (PVB) at thoracotomy results in reducing chronic post-thoracotomy pain compared to thoracic epidural blockade (TEB). To answer this research question with authoritative evidence of clinical and cost effectiveness of PVB, a multi-centre randomised controlled trial with a parallel health economic evaluation is required.

However, feasibility studies are the best way to assess feasibility of a large, expensive full-scale study, and in fact are an almost essential pre-requisite. Conducting feasibility prior to the main study can enhance the likelihood of success of the main study and potentially help to avoid doomed main studies.[28] We have therefore designed this multicentre feasibility study comparing the effectiveness of thoracic epidural blockade and paravertebral blockade in reducing chronic post-thoracotomy pain. This study will evaluate feasibility of a substantive trial and study processes by making the following qualitative and quantitative assessments.

Objectives for the feasibility study

The aims of the feasibility stage are to assess various aspects of the trial design and management and not to determine the relative effectiveness of PVB and TEB.

Primary Objective

To establish the number of patients randomised as a proportion of those eligible to enter the study.

Secondary Objectives

1. Assessment of effectiveness of patient identification and screening processes
2. Identification and analysis of any reasons for failure to recruit patients
3. Examination of the educational materials provided to surgeons and anaesthetists to ensure they are fit for purpose.
4. Assessment of willingness of surgeons and anaesthetists to participate
5. Assessment of the effectiveness of the randomisation process of patients
6. Assessment of sustainability of single-blinding of patients to treatment allocation
7. Evaluation of robustness of data collection processes during patient's hospital stay
8. The proportion of patients followed up at six months
9. Acceptability to and impact on patients of the interventions
10. Assessment of trial processes, including the choice of outcome measures and impact on staff
11. Derivation of the preliminary data from clinical outcome measures to inform the sample size calculation for the substantive study.

TRIAL DESIGN

Design

TOPIC is a randomised controlled trial comparing the effectiveness of thoracic epidural blockade and paravertebral blockade in reducing chronic post-thoracotomy pain. This is a pilot study to evaluate feasibility of a substantive trial and study processes.

Setting

The study started in July 2015 with final follow-up to end December 2016. Two adult thoracic centres, Heart of England NHS Foundation Trust (HEFT) and University Hospital of South Manchester NHS Foundation Trust (UHSM), with a patient case mix and size typical of UK thoracic anaesthetic practice, will take part in this feasibility. Based on National Thoracic Surgery Activity and Outcome Report and local audit data, an estimated total of 500 elective open thoracotomies were performed at BHH (n=400) and at UHSM (n=100) in 2011. All adult patients admitted for elective thoracotomy who fulfil the inclusion and exclusion criteria during the study period will be approached at both sites. The coordinating centre will be based within MIDRU in Birmingham Heartlands Hospital.

Flow of Participants during the trial

The anticipated journey of participants through the trial is depicted in the flow chart as indicated in Figure 1.

All adults undergoing planned elective thoracotomy at study sites fulfilling inclusion and exclusion criteria will be approached and the trial written information sheets will be given to them and the study will be discussed fully. Written Informed consent will be obtained. Patients who consent to participate in the trial will be randomised to either receiving TEB or PVB arm which will be delivered during the patient's surgery by either a Surgeon or Anaesthetist trained in the study protocol. Patient will be randomised on the morning of the surgery. If either surgeon or anaesthetist is not available to deliver the intervention, randomisation will not go ahead.

Pre and post-surgery study data collection will be performed and study questionnaires will be completed, as detailed. Adverse events will be collected throughout the duration of patients' participation in the study. Figure 2 is a summary of investigations and assessment.

Study Eligibility

Inclusion Criteria

- Aged ≥18 years
- Elective open thoracotomy
- Able to understand the study information and provide written informed consent
- American Society of Anaesthesiologists physical status I, II or III
- Not known to be pregnant

Exclusion Criteria

- Known allergy to local anaesthetics;
- Infection near the proposed puncture site;
- Coagulation disorders;
- Thoracic spine disorders
- Chest wall resection
- Emergency thoracic surgery
- Previous thoracotomy
- Likely inability to comply with completion of the study questionnaires

Patient identification and screening procedure

Research staff will work in close liaison with the multidisciplinary team responsible for routine patient care. Patients listed for elective open thoracotomy will be identified and screened for eligibility at clinics prior to their planned surgery. If a patient is screened but is not eligible for the TOPIC trial or consent for randomisation is not given, a record of the case will be kept in the screening log. The log will collect hospital number, patient's initials, date of birth, age, ethnic group, BMI and reason not eligible for the trial. The log should be kept in each study centre's site file and a copy (in an anonymised format – removing initials and hospital number) sent to TOPIC trial office. This will inform recruitment targets. No further information will be collected on ineligible patients or those that have not given consent for randomisation.

Patient recruitment

Ideally consent should be sought under unhurried circumstances when entry criteria are fulfilled. Consent is sought in several stages. We aim to identify patients who will need a planned surgical thoracic operation within the two recruiting study sites. Eligible patients will be identified in clinics prior to surgery. Ethically approved participant information sheet will be given to eligible patients, supported by face to face discussion with the research team and their consultant. The participant information sheet has been developed with feedback from our PPI representatives, and any

ambiguities, or questions frequently asked by those approached, will be collated. This will enable a comprehensive, but clear, participant information sheet to be deployed if we proceed onto a substantive trial.

If patient consents to participate in the study, written informed consent will be obtained by a member of the research team. Enough time will be given to discuss the study, ask any questions before seeking consent. If the patient decides to enter the trial, they will be asked to sign two original copies of the Patient Consent Form which will then be countersigned by the member of the research team taking the consent. The patient will retain one copy of the signed Consent Form. The second copy will be photocopied and the photocopy placed in the patient's medical records whilst the original will be retained in the Investigator Site File.

Participants will be asked to consent to their GP being informed about their participation in the study.

Randomisation

After written informed consent, the patient will be randomised, on the day of surgery, to either thoracic epidural blockade (TEB) or paravertebral blockade (PVB). Participants will be individually randomised into the study in an equal 1:1 ratio. Randomisation will be by a web based randomisation system, with a telephone option available as back-up, managed by the Birmingham Clinical Trials Unit (BCTU).

A 'minimisation' procedure using a computer-based algorithm and incorporating a random element will be used to avoid chance imbalances in the following variables. The variables chosen are:

- Gender
- Age <65 years or ≥65 years
- Centre (Birmingham Heartlands Hospital or University Hospital of South Manchester)
- Thoracotomy for lung cancer resection or for other indication

Using the web-based randomisation service, patients will be allocated to a treatment group. The anaesthetist and surgeon in charge of patient care will be informed of the patient's allocation. A unique study identification number will be assigned to the participant.

Study anaesthetic and analgesic strategies

All study patients will be anaesthetised by experienced thoracic anaesthetists (consultants) who have been trained and deemed competent in both anaesthetic techniques. The study team has worked closely with consultant anaesthetists to develop a suitable training package. Consultant anaesthetists are capable to perform both epidurals and paravertebral blocks however for the purpose of the study, anaesthetists will be asked to perform the techniques to the standard required by study protocol. Two online training videos detailing thoracic epidural and paravertebral blocks have been produced alongside supplementary written step-by-step guide. A copy of the videos is also available in DVD format. All anaesthetists participating in the study must review both video and/or written material and confirm that they are able to perform the techniques according to study

protocol. Further training, if required, will be provided by study-designated trainers at each participating sites who can demonstrate and observe performance if required. All training material will be freely available at each site and will act as a reference for participating anaesthetists and surgeons. Training by participating anaesthetists will be documented in training logs.

To be pragmatic, some variation in technical aspects of block insertion detailed in the training is anticipated, both between experienced thoracic anaesthetists, and those trained for the trial, and between centres, as anaesthetists will use their judgment on the best techniques for each patient. This represents real world variation in anaesthetic practices and will not contribute to bias since randomisation will ensure balance across groups by centre. The location and dose of anaesthetic will be captured on a post-operative case report form (CRF).

Experimental group: Paravertebral blockade

Three single injections, awake or asleep, using 16G/18 G graduated epidural needle with 15ml 0.25% bupivacaine at T3-4, 5-6 and 7-8, will be given pre-operatively. The PVB catheter will be placed at T5 under direct vision by a surgeon at the end of surgery before chest closure. A loading dose of 10ml 0.25% bupivacaine is given before chest closure followed by infusion of 0.125% bupivacaine 0.1-0.25ml/kg/h. See Appendix for further details.

Control group: Thoracic epidural blockade

Usual practice of TEB, awake or asleep, using 16G/18G graduated epidural needle with a catheter inserted at the spinal level supplying the skin at the incision site, a test dose of 3ml of 0.25% bupivacaine, and a loading dose of 0.25% bupivacaine 0.1ml/kg with up to 3mg of diamorphine. This will be followed by infusion of 0.125% bupivacaine with 2mcg/ml fentanyl at 0.1-0.25 ml/kg/h. See Appendix for further details.

Study Treatment Dispensing

All anaesthetics and analgesia will be taken from standard theatre pharmacy stock. As TOPIC does not fall under the Medicines for Human Use (Clinical Trials) regulations 2004, segregated stocks for trial use and specific trial labelling is not required. Temperature monitoring should follow local pharmacy practice and deviations need not be reported to the TOPIC Study Co-ordinator.

Blinding of trial allocations

By the nature of the interventions it is not possible to conceal treatment assignments from surgeons and anaesthetists. Moreover, from a safety aspect, it is vital that the nursing staff caring for the patient know the amount of epidural opiates prescribed before administering systemic opiates, and known adverse events such as hypotension or pruritis expected to arise from the respective anaesthetic approaches.

Every attempt will be made to blind study participants to their group allocation. The epidural or paravertebral block infusion catheter will be taped laterally on the side of operation so no visible difference can be seen by the patient. Infusion pumps used by both groups will also be identical.

Withdrawal from the Trial

Withdrawal from the trial before surgery is a decision of the participant, however, withdrawn patients can bias trial results and reduce the power of the trial to detect important differences, so randomisation will take place as close to the time of surgery as is practical in order to reduce post randomisation withdrawals. Following surgery participants should be encouraged to allow clinical data collection to continue even if they decline to complete further questionnaires.

Cessation of the allocated anaesthetic strategy will also be necessitated in cases where a known serious adverse reaction to the anaesthetic occurs or a suspected unexpected serious adverse reaction occurs.

Protocol Violations

Any incidences of study participants not receiving the anaesthetic strategy allocation by randomisation will be recorded. All study and protocol violations and deviations will be documented in the patients CRF and reported to the Study Sponsor via the Trial Office. Patients will be analysed according to group allocation, by intent-to-treat analysis.

Additional intraoperative analgesia

Supplementary intraoperative analgesia will not be restricted and can follow local policy. Analgesia and doses will be recorded as part of the study in the patients CRF.

Post-operative analgesia

Both groups should continue with TEB/PVB infusion of 0.1-0.25 ml/kg/h bupivacaine, in the first instance for 48 hours post-operatively. All participants will receive regular paracetamol and prophylactic anti-emetics unless contraindicated. Non-steroidal-anti-inflammatory drugs can also be administered if appropriate. All analgesic requirements will be recorded during inpatient follow-up.

For TEB group, intravenous morphine boluses will be prescribed for break-through pain which is not relieved by the epidural top ups. If the epidural is ineffective and no block is evident, the TEB can be reinserted at the discretion of the anaesthetic team. If pain relief is inadequate, morphine PCA (Patient Controlled Analgesia) can be administered.

For PVB group, intravenous morphine boluses followed by morphine PCA will commence on recovery from anaesthesia.

OUTCOMES AND DATA COLLECTION

Patient Recruitment into study

The overall aims of the feasibility are to find out if a larger trial is feasible. The quantitative measurements related to this include

- Proportion of all elective thoracic procedures screened
- Proportion of eligible participants of those screened
- Proportion of eligible participants randomised

In this feasibility study of 2-centres, Heart of England NHS Foundation Trust and University of south Manchester NHS Foundation Trust, there would be an approximate total of 500 elective open thoracotomies over the study period. The plan will be to recruit and randomise as many patients as possible over the 12 month study period. It is expected that between 50 and 75 eligible patients will be recruited from two sites.

Patient identification and screening

We would expect a very high proportion of patients to be screened across both study sites, given that only patients with planned thoracotomy will be included. The proportion of patients screened for eligibility and recorded on a screening log will be assessed and reported as proportion of patients screened from the total number of planned thoracotomies during the study period.

Reasons for failure to recruit

The proportion of patients that were missed, which should be minimal and proportion of patients who decline to take part will be recorded. Patients decline for many reasons, which should be captured whenever possible. We will consent declining patients to a short interview. The reasons for declining will be recorded anonymously and analysed by the research team. If there is a strong patient preference, the substantive trial may not be feasible, similarly if this population is disinterested or conversely, taking part in other trials that preclude concurrent participation.

Educational Materials and Training of surgeons and anaesthetists

Feedback on the appropriateness, value and acceptability of the training will be elicited from the feasibility sites, to enable refinement of the training programme for the substantive study, and to define a minimum competence. The training material will be evaluated for its ease of use should it be used in the substantive study.

Evaluation of willingness of anaesthetists and surgeons to participate

As part of preparation of the study site, all anaesthetists and surgeons in both sites will be approached to evaluate willingness to participate in the trial. The Site PI(s) and the Trial Coordinator will discuss the protocol to ensure that all inclusion/exclusion criteria and technical aspects are well

understood by the participating anaesthetists and surgeons. Patient "vignettes", both typical and unusual, will be presented during this training to establish whether uncertainty exists and therefore randomisation is ethical in all situations, or whether there are somewhere either technique is preferred. Training material will be revised, as per the feedback for use in the substantive study, portraying best practice in approaching and consenting participants.

The study team will also conduct a repeat national survey to assess willingness from the clinical community nationally towards the end of feasibility study.

Effectiveness of Randomisation process

This would be ascertained by the speed in which patients can be randomised and whether important prognostic data can be collected pre-operatively.

Assessment of Data collection process

Assessment and identification will be made for loss of data during in hospital stay to improve data collection process for the substantive trial.

Assessment of sustainability of single blinding of patients to treatment allocation

By the nature of the interventions it is not possible to conceal treatment assignments from surgeons and anaesthetists. Every attempt will be made to blind study participants to their group allocation and various methods may be considered. The patient reported outcomes will be collected remote in time from the acute intervention. There is no reason to suspect that recipients of the randomised intervention have strong pre-conceptions with regard to the relative effectiveness of each analgesic technique. In this feasibility study patients will be asked at 3 and 6 months after surgery via questionnaire which technique they think they received to test if our various methods for patient blinding were effective.

Assessment of follow-up rates

The primary outcome of the substantive study is chronic pain assessed at 6-month post-randomisation. It is therefore vital for the appropriate measures to be in place to minimize the loss of follow-up.

The research team will demonstrate and assist the patient to complete the questionnaires in person when the baseline data is collected. This face-to-face assistance and support in filling the questionnaire will help encourage patients and increase their confidence in completing questionnaires after discharge.

The patient has consented to be contacted by post or by telephone for follow-up purposes. Prior to the follow-up questionnaires being sent to patients at home, their vital status will be confirmed by a research team member from study sites. The contact information and patient status will be faxed

from study sites to BCTU for follow up purposes. Follow up questionnaire will include pain questionnaires, patient satisfaction questionnaire and assessment of single blinding. To be viable as a primary outcome, we would expect to achieve a response rate of 80% of expected patients, using various methods of contact. We should be able to capture 100% of mortality data via NHS tracing services. A withdrawal from follow-up of over 10% would be disappointing. The reasons for loss of follow-up if any will be documented and reported at the end of the feasibility study.

Patient reported outcomes

At baseline and prior to surgery, 5 sets of questionnaires will be completed. These comprise: Visual Analogue Scale score, Brief Pain Inventory interference score (BPI)[29 30], Neuropathic Pain Scale (NPS)[31], Generic health related quality of life (EQ-5D-5L)[32] and Hospital Anxiety and Depression Scale (HADS)[33].

In hospital data collection will include Visual Analogue Scale scores, Brief Pain Inventory, analgesic use, any acute complications conducted on Day 1, Day 2 and Day 3 post-surgery. Using day of surgery as Day 0, Day 1 is defined as the first full calendar day (from 12 midnight) post surgery, Day 2 is second full calendar day, Day 3 is third full calendar day.

On hospital discharge take home analgesia (TTOs), in-hospital mortality, acute complications, unplanned admission to level 2 or level 3 care including organ support and length of level2/level 3 stay, and total length of hospital stay. Assessment and identification will be made for loss of data during in hospital stay to improve data collection process for the substantive trial.

Six sets of questionnaires will be completed prior on hospital discharge and at three and six months post-randomisation: The national registry will be checked to confirm patients status prior to follow up questionnaires being sent at three and six months. These questionnaires are Patient satisfaction questionnaire with their overall care and with their pain relief and question to assess whether patient was aware of treatment allocation, Visual Analogue scale scores, Brief Pain Inventory interference score (BPI)[29 30], Neuropathic Pain Scale (NPS)[31], Generic health related quality of life (EQ-5D-5L)[32] and Hospital Anxiety and Depression Scale (HADS).[33]

Acceptability to and impact on patients

Patient interviews will explore the acceptability of the intervention to patients and any impacts on their stay in hospital and post-discharge. Semi-structured qualitative interviews will be undertaken with up to 30 study patients with representation of patients taking part across the two sites. The interviews will be conducted at 6-8 weeks post-discharge. This will allow for a reasonable recovery period post-surgery and will enable interviews to be undertaken with the small proportion of patients who go on to need chemotherapy, prior to this treatment beginning. The interviews will be done by telephone in order to minimise the disruption to and effort required by patients.

All patients will be eligible for interview and will be selected using maximum variety sampling by age, sex and ethnic group.[34] The need for a maximum variety sample will be balanced against spacing the interviews as evenly as possible across the 12 months of the trial so that any variations in how

the trial is implemented are reflected in the patient sample. Interviews will be conducted until saturation is achieved, which is likely to be around 30 patients.[35]

A framework for the patient interviews will be developed in months 1-3 of the trial set-up period, with reference to the literature on similar trials. The framework will also be discussed with Clinical Research Ambassador Group (CRAG) based within Heart of England NHS Foundation Trust. It will include 5 core questions that will be asked of all patients, which will cover;

- reasons for taking part in the trial
- assessing whether patients knew which anaesthetic strategy they received
- the effectiveness of staff and written communication about the trial
- how the trial impacted on their stay in hospital and at home following discharge
- suggestions for making improvements to the recruitment processes

The semi-structured nature of the interviews will allow patients to raise issues which may not have been anticipated by the research team, and will allow the interviewer to explore any patient concerns in depth. The interviews are expected to last an average of 15-20 minutes, and will be recorded digitally. If during the interviews, any patients indicate that they have unresolved concerns or clinical symptoms, they will be directed to their named research nurse. Similarly, if patients get upset the interviewer will ask for the patient's consent to be contacted by their dedicated research nurse for further discussion.

Telephone interviews will also be undertaken with up to 10 patients who declined to take part in the trial, to explore their reasons for declining and to identify how a larger trial could be adapted to encourage higher rates of participation.

Assessment of trial processes and impact on staff

Semi-structured qualitative interviews with clinical and research staff will be undertaken to explore the effectiveness and efficiency of the trial processes. This will include exploring a number of the secondary outcomes:

- the effectiveness of the patient identification and screening processes
- identification of reasons for failure to recruit patients
- the willingness of surgeons and anaesthetists to take part
- the effectiveness of the randomisation process.

Interviews will also ask for staff ideas for improvement in trial processes, and explore whether there are any unintended consequences of the trial procedure which might have an impact on patient care processes or the organisation and management of care.

Up to 20 staff interviews will be undertaken, which will be spread evenly across the two sites and will include the main clinical and managerial roles affected by the trail. The interviews will be undertaken in the month following the discharge of the last trial patient home. The interviews are expected to last an average of 20-30 minutes, and will be recorded digitallyData Collection and Management

All data for an individual patient will be collected by each Principal Investigator or their delegated nominees and recorded in the study specific data collection forms (CRF). Participants will only be identified through their unique Trial Number allocated at the time of randomisation and their initials. Data will be collected from the time the patient is entered into the trial through their discharge from hospital and up to 6 months post-surgery.

STATISTICS AND DATA ANALYSIS

Sample size calculation

We expect to recruit between 50 and 75 patients depending on the number we find eligible for the study. For example, we estimate that there will be approximately 500 open elective thoracotomies over 12 months from the two sites (Heart of England NHS Foundation Trust and University Hospital of South Manchester NHS Foundation Trust), of which 60% will be eligible, (300). Using our own target criteria of 25% recruited would make 75 participants. This number will allow us to measure the recruitment rate with 95% confidence interval (CI) of width approximately 10%. It will also be enough to estimate the standard deviation (SD) of VAS score with 95% CI of width 7 points (assuming the SD is around 25 points).

Data Analysis

The size of this study will not allow reliable assessment of the effect of the intervention on outcomes and so hypothesis testing is not proposed. Analyses of feasibility and patient reported outcomes will primarily take the form of simple descriptive statistics (e.g. proportions & interquartile ranges, means and standard deviations) and where appropriate, point estimates of effects sizes (e.g. mean differences and relative risks) and associated 95% confidence intervals.

In the first instance, for patient reported outcomes, participants will be kept in the groups they were allocated, regardless of compliance with treatment (intention-to-treat). Analysis will be completed once all patients have completed six month follow-up. A Statistical Analysis Plan will be generated for review by the Trial Oversight Committee before any analysis takes place.

Handling Missing Data

There is a potential for some missing data to occur at follow-up, however, a member of the research team will contact patients for any missing data (for example questionnaire) via telephone and post. Where patients attend for follow-up clinic, the potential for missing data will again be limited, and the secondary outcome data will also be collected at this point. Imputation of missing responses is not proposed for patient reported outcome as this is not a definitive trial and no hypothesis testing will be performed

Data Management and Quality Assurance

Data management and confidentiality

Personal data and sensitive information required for the TOPIC feasibility study will be collected directly from trial participants and hospital notes on data collection forms, coded with the participant's unique trial number and initials. All other patient identifiable information will be removed. Participants will be asked for their consent to transfer this information, including their

name and contact address for follow up to the BCTU office based in University of Birmingham. The data collected will be entered onto a secure computer database by BCTU staff. This database, once completed will be locked under the direction of Lee Middleton (Senior Statistician) for analysis.

All personal information received in paper format for the trial will be held securely and treated as strictly confidential according to NHS policies. All staff involved in the study (clinical, academic, BCTU) share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be stored on a secure server at Birmingham Clinical Trials Unit (BCTU) under the provisions of the Data Protection Act and/or applicable laws and regulations. The trial coordinator, study statistician and the data manager will have access to the database until completion of the analysis. Data may be accessed by external regulatory agencies and the Study Sponsor representatives and permission for this access will be documented within the participants consent form.

Data Quality Assurance and Validation

The study will adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the study data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry of paper questionnaires will be periodically undertaken on small sub-samples. The trial statistician (Lee Middleton) will regularly check the balance of allocations by the stratification variables. Source data verification will only be employed if there is reason to believe data quality has been compromised, and then only in a sub-set of practices.

Quality assurance will begin with a clearly documented staff training programme. A register of staff who have been trained, and their competence assessed will be maintained, and only staff whose names appear on this list will be permitted to undertake study procedures. Staff will also receive regular update training and periodic reassessment of their competence. Real-time reports will be available to staff indicating missing test and questionnaire data for all participants at that centre. This will be supplemented by regular reminders from the TOPIC Trial Office for incomplete data.

Monitoring and Audit

The study will be monitored and/or audited by Heart of England NHS Foundation Trust under their remit as Sponsor and other regulatory bodies to ensure adherence to Good Clinical Practice and the NHS Research Governance Framework for Health and Social Care (2nd edition).

Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Co-ordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of study data as an on-going activity.

The first study participant who has been randomised, received surgery and completed up to the 72 hour follow up stage of the protocol will be monitored by the Sponsors QA Manager to ensure the protocol is fit for purpose and review protocol adherence. Monitoring of study participants by the

Sponsors QA manager will then occur at random intervals throughout the study based on recruitment.

Study conduct will be subject to systems audit of the Study Record for inclusion of essential documents; permissions to conduct the trial; Study Delegation Log; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs. This will be led by the Trial co-ordinator and reported back to the Sponsor and the Sponsorship Oversight Committee.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10%) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the study database will be checked. Where corrections are required these will carry a full audit trail and justification.

Study data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

Long-term storage of data

Trial data will be stored archived after the formal closure of the trial in accordance with archive policy and for the appropriate duration as per current legislation.

The Computer database may be stored within the BCTU and will be processed according to their trial archiving policies.

SPONSORSHIP AND INDEMNITY

Heart of England NHS Foundation Trust will act as the Sponsor to this study. Delegated responsibilities will be assigned to the Chief Investigator and the NHS Trust(s) taking part in this study. The non-commercial model clinical trials agreement will be used with all participating sites detailing their local responsibilities.

Heart of England NHS Foundation Trust holds standard NHS Hospital indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

REGULATORY APPROVALS

The study has obtained ethical approval from NHS Research Ethics Committee (REC number 14/EM/1280).

FUNDING

This work was supported by National Institute for Health Research for Patient Benefit Programme grant number (PB-PG-0213-30126).

STUDY DISSEMINATION

This feasibility study is designed to identify if a substantive trial is possible. Although a definitive answer to the key research question on effectiveness of paravertebral blockade on CPTP cannot be provided, the findings of this feasibility study will be of scientific interest to others in their own right. The feasibility study will be registered on clinical trials database (www.clinicaltrials.gov). We plan the dissemination strategy in three aspects. The first will ensure that patients and health professionals are informed of the feasibility findings; the second will engage multi-disciplinary professionals to support a proposal of a definitive RCT and the third will be to resubmit for a full HTA application dependant on the success of the feasibility study.

AUTHORS' CONTRIBUTIONS

The authors contributed equally to writing of the protocol.

FUNDING STATEMENT

This work was supported by National Institute for Health Research for Patient Benefit Programme grant number (PB-PG-0213-30126).

COMPETING INTERESTS STATEMENT.

The authors declare no conflict of interest.

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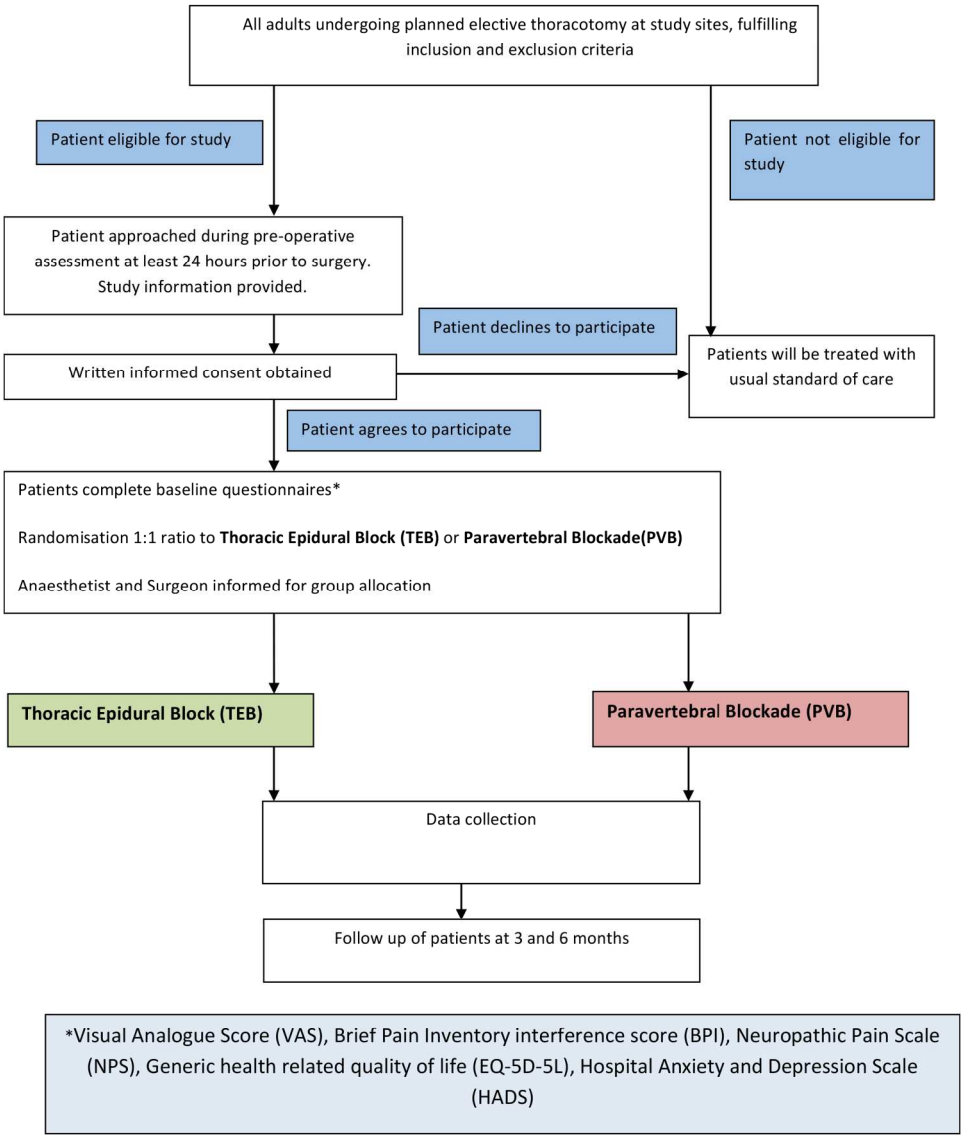
LEGENDS

Figure 1 Flow of Participants during the Trial

Figure 2 Summary of investigations and Assessments

Day one is first full calendar (from 12 midnight) post surgery, Day two is second full calendar day, Day three is third full calendar day.

Figure 1 Flow of Participants during the Trial



218x273mm (300 x 300 DPI)

	Baseline	In-hospital				Follow-up		
	Clinic appointment prior to surgery	Intra-operative	Day one*	Day two*	Day three*	Hospital discharge	Three months	Six months
Eligibility and written informed consent[1]	X							
Demographic data	X							
Previous Medical History	X							
Randomisation	X Day of surgery							
TEB/PVB insertion data		X						
Other intraoperative data		X						
Post operative observations			X	X	X	X		
Post-operative pulmonary complications			X	X	X	X		
Visual Analogue Scale score	X		X	X	X	X	X	X
Brief Pain Inventory	X		X	X	X	X	X	X
Post-operative analgesic use			X	X	X	X	X	X
Acute Complications			X	X	X	X		
Hospital Length of Stay						X		
Mortality						If applicable		
Neuropathic Pain Scale	X					X	X	X
Discharge data and histology data						X		
EQ-5D-5L	X					X	X	X
Hospital Anxiety Depression Scale	X					X	X	X
Patient satisfaction						X	X	X
Adverse Events	If applicable							
Protocol deviations	If applicable							

Figure 2 Table of summary of investigations and assessments

95x52mm (300 x 300 DPI)

APPENDIX

Thoracic Epidural Blockade Template

General points on Insertion of TEB Catheter

- Institute full monitoring according to AAGBI guidelines.
- TEB can be inserted in patients awake or asleep, sitting or in lateral position
- Catheter insertion should be at mid thoracic level (T6-T7 or T7-T8)

Intra operative Utilisation of TEB catheter

- First dose is given with 3-5 ml of 0.25% bupivacaine with 2-3 mgs of diamorphine. 2mg for patients <50kg, 2.5mg for patients 50-65kg, 3mg for patients >65kg. Dose of diamorphine should be titrated if patient is more than 75 years of age.
- This mixture provides adequate analgesia for the initial skin incision and further boluses of local anaesthetics are only given if patient's physiological parameters warrants.
- Towards the end of the operation, we start our epidural infusion of 0.125% bupivacaine and 4mcg/ml fentanyl at a rate 0.1-0.25 ml/kg/h.
- All patients receive intravenous Paracetamol and NSAIDs if there are no contraindications.

Post operative Utilisation of TEB catheter

- The patient is assessed in recovery and if they have pain, further titrated boluses of 3-5mls of epidural mixture (0.125% bupivacaine with 4mcg/ml fentanyl) is given for break through pain. Bolus can be repeated.
- All thoracotomy patients are looked after in a thoracic surgical HDU. The acute pain team reviews the patients regularly and the epidural is stepped down to oral/IV analgesics after 48 hours.
- Patients are prescribed regular oral analgesics such as paracetamol and NSAIDS.
- Nursing staff regularly assesses the block height and epidural rate is titrated as per the local pain protocol.
- If the blood pressure is persistently low and other surgical causes of low blood pressure have been ruled out, the diagnosis of epidural associated hypotension is made. Metaraminol infusion is then started at 0.5-1.5 micrograms/kg body wt min^{-1} (Appendix). This avoids the need for CVC line perioperatively and restricts the amount of fluid administered.

- The pain scores at rest and when mobile, motor block, postoperative nausea and vomiting and sedation scores are also assessed regularly and recorded.

- During the post operative period any complications of epidural analgesia are noted by surgical nursing staff. Advice from the acute pain team and the anaesthetist should be sought if pain control is problematic.

- In the event when epidural is deemed ineffective, morphine boluses including morphine PCA should be prescribed.

Paravertebral Blockade Template

General points on PVB and catheter insertion

- Institute full monitoring according to AAGBI guidelines.
- PVB can be performed on patients awake or asleep, sitting or in lateral position (we prefer lateral position, asleep)
- 3 preoperative PVB injection using landmark technique at the level of T4-5, T7-8, T9-10 followed by surgical catheter insertion after the thoracotomy

Intra operative Utilisation of PVB

- 15 ml 0.25% bupivacaine with or without adrenaline (1:200000-400000) to be used for each preincisional block using landmark technique ("predetermined distance technique")
- This concentration and volume should provide adequate spread and analgesia for the initial skin incision on an patient under light general anaesthesia, who is otherwise able to tolerate one lung anaesthesia.
- We do not assume that the surgical analgesia provided by the local injections lasts longer than 2-4 hours, therefore the surgical paravertebral/epipleural catheter insertion should be performed after the thoracotomy in order to make continuous infusion possible. Within 2 hours, 10 ml 0.25% bupivacaine bolus to be administered via the catheter followed by 0.25% bupivacaine infusion with 10 ml/hour until the end of the operation.
- All patients receive intravenous Paracetamol and/or NSAIDs if there are no contraindications. The paravertebral group should have 1mg/ml morphine PCA infusion with 5 minutes lockout time for rescue pain-relief.

Post operative Utilisation of TEB catheter

- The patient is assessed in recovery and if they have pain the rate of the infusion can be changed in order to provide adequate pain-relief (0-15 ml/hour, depending on the patients' bodyweight: max. 2 mg/kg/4hour bupivacaine dose). In case of the need of higher dose 5 ml bolus should be administered first.
- All thoracotomy patients are looked after in a thoracic surgical HDU. The acute pain team reviews the patients regularly and the epipleural/paravertebral is stepped down to oral/IV analgesics after 48 hours.
- Patients are prescribed regular oral analgesics such as paracetamol and/or NSAIDS; iv morphine PCA should be available for rescue pain-relief (see above).

- Nursing staff regularly assess the pain score, neurological status, physiological parameters and the area of the anaesthetized chest wall. If the anaesthetized area unnecessarily large the infusion rate should be decreased by 2 ml/hours. The lowest rate should not be lower than 5 ml/hours. If the pain-relief is inadequate 5 ml bolus 0.25% bupivacaine should be administered and the rate should be increased back to the last adequate rate and continue with this rate till the catheter removal.

- If the blood pressure is persistently low or there any other sign of epidural spread or local anaesthetic toxicity the infusion to be stopped immediately and the patient should be managed according to the guidelines. These events will exclude the particular patient from the study.

- The pain scores at rest and when mobile, motor block, postoperative nausea and vomiting and sedation scores are also assessed regularly and recorded.

- During the post operative period any complications of epipleural/paravertebral infusion are noted by nursing staff. Advice from the acute pain team and the anaesthetist should be sought if pain control if problematic.

- In the event when epipleural/paravertebral infusion is deemed ineffective, morphine boluses including morphine PCA should be prescribed.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12, 15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18, 20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.