TRIAL PROTOCOL

TOPIC 2

A Randomised Controlled Trial to investigate the effectiveness of ThOracic Epidural and Paravertebral Blockade In reducing Chronic Post- Thoracotomy Pain: 2

This protocol has regard for the HRA guidance and is compliant with SPIRIT

Sponsor Reference No.	**RG_17-255**
Version Number:	5.0
Version Date:	08-Oct-2021
IRAS:	**248427**

Protocol development

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Date of amendment	Protocol version no.	Type of amendment	Summary of amendment
1	04/03/2019	2.0	Substantial	• Update DMC membership • Update to TSC membership • Update to TMG and collaborators • Update to TSC membership • Update of trial office contact detail • Update to trial summary so it is consistent with updates to other sections • Update to trial schema • Update to funding and support in kind section • Update eligibility criteria for clarity (section 4.2) • Removal of statement that patient will be approached at least 24 hours prior to surgery as this was stated in error (section 1.2.3) • Clarification that EQ5D5L will be collected at 3 months (section 2.2.3) • Removal of statement that QRI consent forms will be shared with QRI team in Bristol (section 5.1.2) • Clarification that patient should ideally be randomised on day of surgery or the working day prior to surgery (section 6.2.2) • Removal of unnecessary statement: 'Details of the anaesthesia used during the intervention will be recorded on the appropriate CRF to confirm that they comply with above schedules' (section 7.2) • Correction of VAS scores in secondary outcome measures for incidence of severe and moderate pain (section 8.2): • Correction of acute phase outcome in table 8.2 in line with patient completed booklet content • Addition of section 8.3 to outline study procedures • Update of schedule of assessments to extend baseline assessments to up to 28 days prior to intervention, addition of medical history at baseline,

				addition of day 0 column for clarification, addition of notes for clarity. • Removal of statement 'The participant wishes to withdraw completely (i.e. from trial treatment and all follow up) and is not willing to have any of their data, including that already collected, to be used in any future trial analysis' in section 8.5 • Update to AE definitions table for clarity (section 9.1) • Addition of section 9.5 reporting period to make it clear that reporting period of SAEs is from date of intervention to 30 days after intervention • Update to adverse events requiring reporting in TOPIC 2 section to list that complications of regional anaesthesia are be collected as part of the targeted AE dataset. (section 9.3) • Updates to expedited and non expedited reporting sections for clarity (sections 9.4.2 and 9.4.3) • Update to assessment of relatedness to make it clear that PI or medically qualified delegate should define severity and causality of SAE (section 9.7) • Update to protocol defined expected AEs section to clarify that expected pulmonary complications are defined in appendix E (section 9.8.1) • Update to source data definition table (section 10.1) • Update to data collection form tables to reflect full CRF, insertion of statement that CRF will be electronic records rather than paper (apart from patient completed booklets and serious adverse event forms), insertion of statement describing use of paper forms as worksheets for clarity. Addition of section detailing expectations for data return and escalation process if data is not returned according to the expected timeframe (section 10.2). • Update to data management (Section 10.4) to clarify which data will be entered electronically at site and which data will be paper based and entered at the trial office.

				Clarification regarding self-evident corrections that can be performed at the trial office.
2	12-Mar-2020	3.0a	Substantial	• Updates to DMC, TSC, TMG and collaborators • Update to randomisation website link • Update to trial intervention training section for clarity (section 7). • Corrections and update to schedule of assessments. • Update to participant withdrawal section to make it clear that if following randomisation participant does not go on to have a thoracotomy they should be withdrawn (section 8.5). • Update of term 'incidence of CPTP' to 'presence of CPTP' throughout protocol in terms of objectives/outcomes. • Update to thoracotomy for lung cancer resection or for other indication randomisation variable for clarity. • Update to adverse event reporting section to define events of known consequence of thoracic surgery. Protocol defined expected events that meet the SAE criteria and occur during the post surgery admission will be collected in the acute dataset rather than SAE form (section 9). • Update to section 9.3 to make it clear that severity of all complications that are referred to will be classified according to the Seeley Systematic Classification of Morbidity and Mortality After Thoracic Surgery (TM &M) Classification of Severity • Update to data collection form table (table 5). • Update to onsite monitoring section to expand criteria for triggering onsite monitoring visit (section 11.2.1). • Update to analyses of outcome measures section to make it clear that patients that do not go on to have surgery will not be included in the intention to treat analysis. • Update to primary outcome measure section in statistical considerations to make the

				primary outcome clear (section 13.2). • Addition of economic analysis section (section 13.6). • Update to trial steering committee section to correct duration of TSC meetings until full publication of trial (section 14.4). • Update to reference list. • Update to title of appendix A and B.
3	23-Jul-2020	V4.0	Substantial	• For clarity, addition of statement that PIS can be posted to patient • Minor update to PVB intervention section 7.1.2 for clarity. • Update to section 9.4.1 to correct typo. • Minor correction to table 5 • Addition of section 13.3.
4	08-Oct-2021	V5.0	Substantial	• Section 6.2.3 minor correction regarding screening log location which is held electronically on the trial database and will be printed and filed in the ISF at the end of recruitment. • Section 7.1 addition of statement for clarity. • Correction to section 10.4 and 10.6. • Updated summary of amendment table for amendment 3. • Addition of event to section 9.8.1 • Minor clarifications in section 8 • Minor update to section 6.1 • Update to section 9.2 to make the documentation of AEs in terms of the assessment of severity and seriousness and also of causality (relatedness) in relation to the intervention(s) a recommendation. • Minor update to section 9.8 for clarity • Addition of further protocol defined expected events to section 9.8.1 • Update to section 6.4 to remove unnecessary statement • Minor update to section 10.1 source data definitions • Update to section 10.2 to add that PI delegates can sign CRF to confirm data accuracy • Minor grammatical updates throughout

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Funder (s) (Names and contact details of all organisations providing funding and/or support in kind for this trial)	**Financial and non-financial support given:**
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The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, Health Education England or the Department of Health and Social Care. The funder had no role with respect to trial design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.	

Protocol Sign Off

CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.

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

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

This protocol has been approved by:

Trial Name:	TOPIC 2
Protocol Version Number:	Version 5.0
Protocol Version Date:	08-Oct-2021
CI Name:	Prof Fang Gao Smith
Trial Role:	Chief Investigator
Signature and date:	Fang Gao Smith 05/11/2021

Sponsor statement:

By signing the IRAS form for this trial, University of Birmingham, acting as sponsor of this trial confirm approval of this protocol.

This protocol describes the TOPIC 2 trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the TOPIC 2 trial. The trial will be conducted in accordance with the protocol and the principals of Good Clinical Practice, the General Data Protection Regulation and Data Protection Act 2018, and UK Policy Framework For Health And Social Care Research, 2017. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

PI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.

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

This protocol has been approved by:

Trial Name: Protocol Version Number: Protocol Version Date:	TOPIC 2 Version: 5.0 08-Oct-2021
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ABBREVIATIONS

Abbreviation	Term
ACTA	Association of Cardiothoracic Anaesthetists
AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
BCTU	Birmingham Clinical Trials Unit
BPI	Brief Pain Inventory
CI	Chief Investigator
CRAG	Clinical Research Ambassador Group
CRF	Case Report Form
CPTP	Chronic Post-Thoracotomy Pain
ESTS	European Society of Thoracic Surgeons
EQ-5D-5L	Euroqol questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HDU	High Dependency Unit
HEFT	Heart of England NHS Foundation Trust
HRA	Health Research Authority
ICU	Intensive Care Unit
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
NHS	National Health Service
PCA	Patient Controlled Analgesia
PI	Principal Investigator
PIS	Participant Information Sheet
PoP	Post-operative Pneumonia
PPC	Post-operative Pulmonary Complications

PSC	Post-operative Surgical Complications
PPI	Patient and Public Involvement
PVB	Paravertebral Blockade
QA	Quality Assurance
QRI	Quintet Recruitment Intervention
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SF-MPQ-2	Short Form McGill Pain Score questionnaire
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEB	Thoracic Epidural Blockade
UoB	University of Birmingham
UK	United Kingdom
VAS	Visual Analogue Scale

DEFINITIONS

Term	Abbreviation	Description
Chronic post-thoracotomy pain	CPTP	Pain lasting for at least 3 months
Post-operative Surgical complications	PSC	*Occurrence* as per ESTS 'major cardiopulmonary complications' definitions (see Appendix C) and *Severity* classified as per the 'Thoracic Morbidity and Mortality (TMM) classification' (See Appendix D)
Post-operative Pneumonia	PoP	Covered by the SteP COMPAC consensus definition See Appendix E
Post-operative Pulmonary complications	PPC	As per SteP COMPAC consensus definition See Appendix E
Post-operative Respiratory Failure	PRF	Covered by the SteP COMPAC consensus definition See Appendix E

TRIAL SUMMARY TOPIC 2

Objectives

Primary Objective: to test the hypothesis that in adult patients undergoing elective open thoracotomy, the use of paravertebral blockade (PVB) for peri-operative pain relief reduces the presence of chronic pain at six months post randomisation by at least 10% compared with thoracic epidural blockade (TEB).

Secondary objectives:

- To compare the effectiveness of PVB versus TEB in terms of quality of life, neuropathic pain symptoms, symptoms of anxiety/depression and patients satisfaction up to 12 months following surgery.
- To compare the effectiveness of PVB versus TEB in terms of acute pain control up to 72 hours following surgery, incidence of post-operative major and minor complications and length of post-operative hospital stay.
- To analyse the costs and effectiveness of PVB compared with TEB.

Trial Design: TOPIC 2 is a multi-centre, open label, parallel group, superiority randomised controlled trial, with an internal pilot, of 1026 adult (≥18 years old) thoracotomy patients in a 1:1 ratio.

Participant Population and Sample Size: 1026 Consenting adults undergoing elective open thoracotomy, in the UK.

Setting: At least twenty large adult UK thoracic centres with a track record of successful recruitment to clinical trials and typical patient case mix.

Duration: 54 months

Eligibility Criteria

Inclusion:

- Aged ≥18 years
- Elective open thoracotomy
- Able to provide written informed consent
- Willingness to complete trial questionnaires up until 12 months post randomisation

Exclusion:

- Contraindication to TEB or PVB e.g. known allergy to local anaesthetics; infection near the proposed puncture site; coagulation disorders, thoracic spine disorders
- Rib/chest wall resection or planned pleurectomy
- Previous thoracotomy on the same side
- Median sternotomy within 90 days

Interventions

Two existing peri-operative analgesic techniques: i) PVB: three pre-incision injections followed by placement of catheter; ii) TEB placed pre-incision: usual practice

Outcome Measures

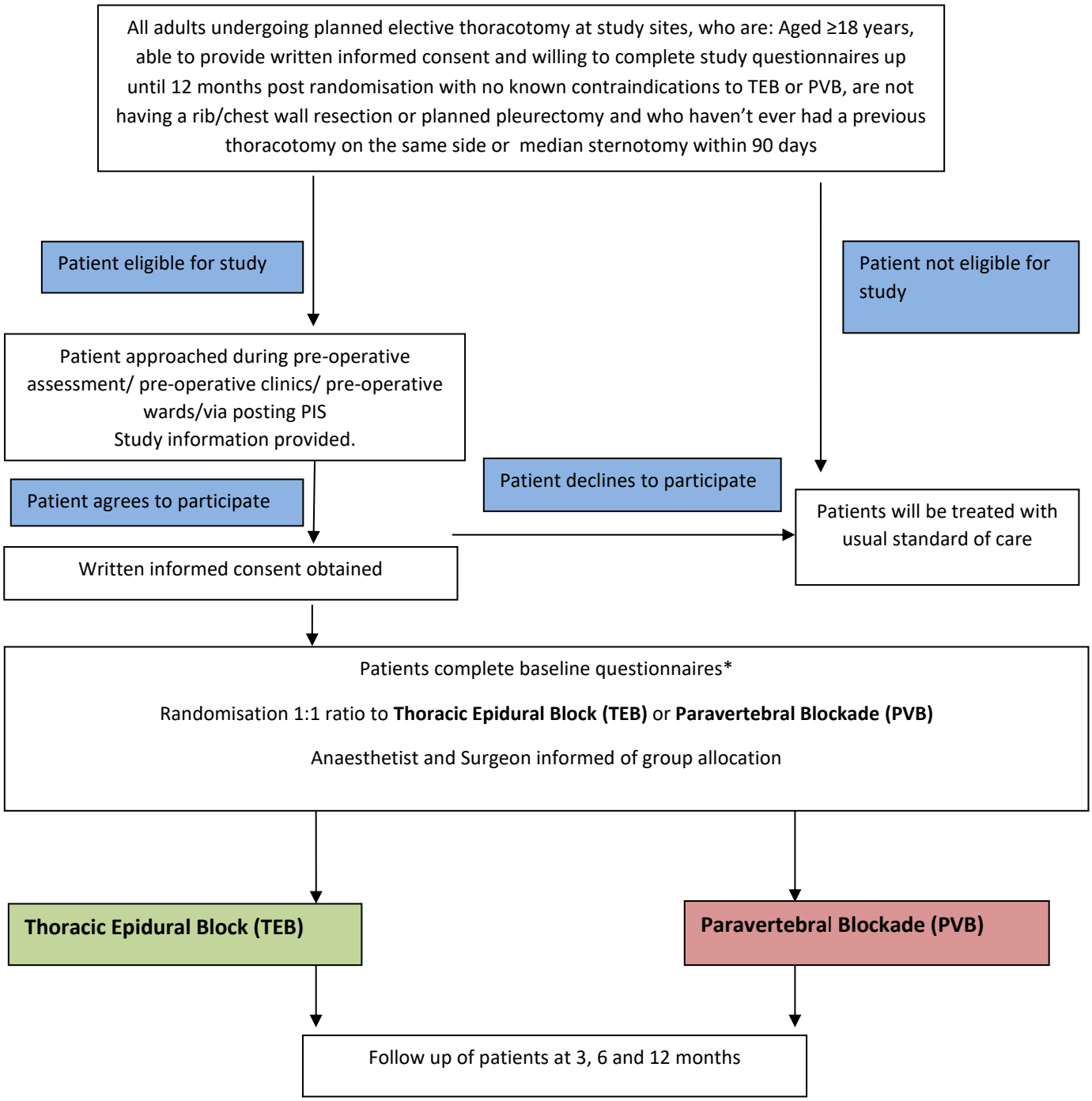
Primary outcome: Presence of CPTP at 6 months post-randomisation. Participants will be asked to indicate their 'worst chest pain over the last week' on a visual analogue scale (VAS; 0-100). Presence of CPTP will be taken to be a score greater or equal to 40 indicating at least a moderate level of pain.

Secondary outcomes measured at, 3, 6 and 12 months post randomisation:

There are a number of secondary outcome measures from the time of randomisation. The following is a non-exhaustive list. For a full list please refer to the TOPIC 2 protocol, section 8.2.

- Complications of regional analgesia
- Occurrence and severity of surgical complications until discharge from hospital
- post-operative pulmonary complications (PPCs) until discharge from hospital
- critical care admission (levels 2 and 3)
- mortality (reported for all deaths due to all causes)
- analgesic use
- acute pain (during initial trial admission), pain at discharge from hospital and chronic pain at 3, 6 and 12 months post randomisation
- resource use and cost data (resource use intraoperatively, during and following hospital admission, and at 3, 6 and 12 months post randomisation)
- general health-related quality of life (by EQ-5D-5L, completed by the participant at discharge and at 3, 6 and 12 months)
- mental health state (measured by HADS, completed by the participant at discharge and at 3,6 and 12 months).
- Patient satisfaction (by Likert scale, completed by the participant at discharge and at 3,6 and 12 months)
- Serious Adverse Events

Trial Schema



*Visual Analogue Score (VAS), Brief Pain Inventory interference score (BPI), Short Form McGill Pain Score (SF-MPQ2), Generic health related quality of life (EQ-5D-5L), Hospital Anxiety and Depression Scale (HADS)

1. BACKGROUND AND RATIONALE

1.1 Background

Surgery through the side of the chest (thoracotomy), most commonly to treat lung cancer,[1] can cause pain post-operatively that can last months or years and an estimated 7200 thoracotomies are performed annually in the UK. It is considered one of the most painful surgical procedures due to tissue, muscle and nerve damage from the incision and wound retraction. Inevitable wound movement during respiration after surgery and intercostal traumatic nerve injury can result in a high risk of persistent pain for months after surgery.[2-4] This Chronic Post-Thoracotomy Pain (CPTP) can be severe and debilitating to patients, leading to more frequent GP visits, anxiety, depression, time off sick and unemployment. The presence of this CPTP defined as pain that recurs or persists at least two months following the surgery)[5] has been reported to be as high as 50%. [6] CPTP is a burden to the NHS that is set to increase as lung operations over the last decade have gone up by 60%.

Two main analgesic techniques are commonly used for perioperative pain control during thoracotomy. A thoracic epidural block (TEB) blocks nerves in the chest, bilaterally, at the spinal cord level. It acts by reducing onward transmission of painful nerve signals but may not abolish them completely.[7, 8] Paravertebral blockade (PVB) involves injecting local anaesthetic into the paravertebral space on the side of surgery and may completely block painful nerve signals from reaching the spinal cord.[9, 10] This total blockade of nerve signals could remove the stimulus for 'central sensitisation' which underpins the formation of chronic pain pathways. PVB could be uniquely effective in preventing long-term pain[11], and there is evidence from a recent trial of two techniques in breast surgery to support this premise.[12]

With limited current evidence to dictate the most effective choice of analgesic technique in preventing CPTP, current UK practice varies greatly.[13] A recent Cochrane Review recommended that a high quality randomised controlled trial (RCT) to compare TEB and PVB with the primary outcome of chronic pain is urgently needed.[14] Our two-year NIHR-RfPB funded pilot trial [15] has completed. It randomised 69 patients, with excellent adherence, demonstrating that a larger trial is feasible in terms of recruitment and retention. Now is the ideal time to build on our momentum and launch a substantive trial that conclusively answers this important question.

Regarding short-term benefits, systematic reviews and meta-analyses supported the use of PVB over TEB, with evidence that PVB provides equivalent analgesia to TEB for acute pain and has a lower failure rate.[16] PVB is associated with fewer pulmonary complications, less urinary retention, hypotension and nausea/vomiting.[17, 18] Many subsequent trials [19-21] (total n=244) supported these conclusions, with the exception of a single trial finding the use of rescue pain relief was significantly higher in PVB compared to TEB (median morphine consumption 9 vs 36 mg, p= 0.003).[22] The most recent meta-analysis[23] including 12 trials of 541 patients and another meta-analysis of 18 trials[24] with a total of 777 patients reinforced PVB effectiveness. In multicentre UK observational data, PVB was associated with significantly lower major post-operative complications (23% vs 35%) and fewer unexpected

intensive care unit (ICU) admissions (8% vs 18%) compared with TEB.[25, 26] These data imply potential implications for the NHS in terms of cost savings.

Pain can often persist after thoracotomy and the presence of chronic pain is high, with studies revealing that 30% to 50% of patients still experience pain up to five years after surgery.[27, 28] The exact mechanism of chronic post-thoracotomy pain is unknown but intercostal nerve damage at thoracotomy is believed to be a major factor, as demonstrated by neurophysiological studies.[29] Electromyography and somatosensory evoked responses demonstrated that intercostal nerve damage led to a decreased pain threshold of the operative scar. A 'wind up' phenomenon of repeated stimulation of peripheral nerve fibres can cause a wide range of nerve fibres to become hyper-excitable and is associated with chronic pain.

1.2 **Trial Rationale**

CPTP is all too common; a systematic review and meta-analysis reported rates up to 50% at 3 and 6 months post-surgery[6] ; a rate largely unchanged from the 1990s to the present day. CPTP is disabling; impairing normal daily activity in up to 66% of patients for at least a year [27].

"What can we do to stop patients developing chronic pain after surgery?" was identified as a top 10 research priority by the James Lind Alliance through the Anaesthesia and Perioperative Care Priority Setting Partnership, involving 25 professional and 20 patients/carer stakeholder organisations in 2015. These were refined from 1,500 suggestions. As clinicians and researchers we have a moral and scientific duty to investigate treatments to prevent or reduce chronic post-surgery pain urgently.

Identifying cost-effective ways of preventing CPTP is vital from an NHS perspective. Patients with CPTP consume significantly more NHS resources than matched patients without CPTP, as 90% of the affected patients required prescription medications for pain and anxiety, whilst 30% received specialist treatments for chronic pain [27]. CPTP is associated with loss of productivity: 40% of patients experienced some level of disruption in their employment status, including reduced working time, unemployment or early retirement [28]. There are no proven primary preventative treatments of CPTP other than supportive perioperative care.

Aggressive management of acute pain resulting from thoracotomy may reduce the likelihood of developing chronic pain.[16] There is some evidence that blocking the nerves as they emerge from the spinal column (paravertebral block) may be associated with a lower risk of major complications in thoracic surgery but previous systematic reviews of analgesic techniques in thoracic surgery have only evaluated short-term complications.[17-19] The effect of TEB or PVB on (long-term) chronic pain is very limited. The Cochrane review only found two studies and the numbers were too low (only 150 patients randomised in total) to provide evidence to support either analgesic technique.[30, 31] In summary, the existing evidence is insufficient to be able to guide practice on which technique is preferable with regards to chronic pain.

1.2.1 Justification for participant population

People experience pain differently to one another and to be sure that the trial answers the question definitively we are proposing to conduct a large clinical trial of 1026 adult participants in 20 UK thoracic centres.

1.2.2 Justification for design

Randomised controlled trials are considered the "gold standard" for evidence-based medicine. Because of the nature of the procedure it is not possible to conceal the team performing the procedure from the allocation (see section 6.4 for details) but they will not know in advance which of the allocated treatments will be received and therefore selection bias will be removed.

1.2.3 Choice of intervention

TEB has long been regarded as the 'gold standard' technique of pain relief for thoracotomy; however this dogma has recently been challenged from an overview of the literature on trends and new evidence in the management of acute and chronic post-thoracotomy pain from 2005 to 2015 [22].

At the present time, both TEB and PVB are routinely used in the UK to provide pain relief for patients undergoing elective open thoracotomy. In **TOPIC 2** the interventional arm will be peri-operative pain relief using PVB and the comparator arm will be peri-operative pain relief using TEB.

Post-operatively patients will receive analgesia in line with current practice.

1.2.4 Embedded Qualitative Recruitment Intervention Sub-study

A QuinteT Recruitment Intervention (QRI)[32] will be integrated in **TOPIC 2** in the first 12 months of recruitment, with the aim of optimising recruitment and informed consent. Recruitment may be challenging if clinicians, nurses, or patients have strong preferences for TEB or PVB. The QRI, led by collaborators from the University of Bristol, assimilates investigation of generic and centre-specific recruitment challenges, with a combination of pre-emptive and responsive feedback/training.

The QRI uses novel qualitative and mixed-method approaches pioneered during the NIHR HTA-funded ProtecT (Prostate testing for cancer and Treatment) study[33] These methods have since been refined and applied to several other RCTs in different clinical contexts, all of which have led to insights about recruitment issues [34] and the development of recruitment strategies [32, 35].

2. AIMS AND OBJECTIVES

2.1. Pilot Phase Stop/go criteria

In the first 12 months from the first site being opened to achieve the following:

- Accrual of 218 patients
- At least 13 sites open to accrual
- At least 70% of sites which are open to accrual successfully recruiting a patient

2.2. Main Trial Objectives

2.2.1. Primary Objective

To test the hypothesis that in adult patients undergoing elective open thoracotomy, the use of paravertebral blockade for peri-operative pain relief reduces the presence of chronic pain at six months post randomisation by at least 10% compared with thoracic epidural blockade.

2.2.2. Secondary objectives

- To compare the effectiveness of PVB versus TEB in terms of quality of life, neuropathic pain symptoms, symptoms of anxiety/depression and patients satisfaction up to 12 months following surgery.
- To compare the effectiveness of PVB versus TEB in terms of acute pain control up to 72 hours following surgery, incidence of post-operative major and minor complications and length of post-operative hospital stay.
- To analyse the costs and effectiveness of PVB compared with TEB.

The above will be measured at 3, 6 and 12 months post randomisation

2.2.3. Economic Objectives

To compare the costs and outcomes associated with the current standard analgesic, TEB, with those of PVB. Resource use data will be collected prospectively to estimate the costs associated with both types of analgesic during surgery, immediately after surgery and in the follow-up period. The resource use to be monitored will include:

- Pre-operative care
- Analgesic use, staffing costs and other treatment costs during surgery
- Post-procedure treatment costs (including days in Intensive Care Unit/High Dependence Unit (ICU/HDU)
- Post-discharge health resource use (eg. associated with hospital readmissions and/or chronic pain management)
- Productivity loss
- Participant out-of-pocket expenses

Information on unit costs or prices will be sourced to attach to each resource use item, to enable an overall cost per patient to be calculated [36].

Resource use data will be captured via a variety of mechanisms. Firstly, within the trial resource use and costs within the hospital setting will be captured for each patient using trial specific CRFs. NHS resource use following hospital discharge will be captured via a patient questionnaire; this will include the use of medication for pain management, hospital inpatient days, GP visits and other resource use. We will also capture patient costs associated with surgery and post-thoracotomy pain in terms of the time and resources associated with attending hospital appointments, and any impacts on employment or care-giving responsibilities.

Health-related quality of life data will be collected using the EQ5D-5L instrument which is widely used and is validated for patients with chronic pain [37]. The instrument will be administered to compare changes in health-related quality of life for the intervention and control arms, at baseline, then at 3 months, 6 months and 12 months post-randomisation.

2.2.4. QRI Objectives (The Information Study)

A QuinteT Recruitment Intervention (QRI)[32] will be integrated in **TOPIC 2** in the first 12 months of recruitment. It aims to understand the **TOPIC 2** recruitment process and how this operates in clinical centres with the intention of developing and implementing of recruitment initiative strategies (see section 3.4). This is referred to as the Information Study.

3. TRIAL DESIGN AND SETTING

3.1. Trial Design

TOPIC 2 is a multi-centre, open-label, parallel group, superiority randomised controlled trial, with an internal pilot, of 1026 adult (≥18 years old) thoracotomy patients in a 1:1 ratio. Patients will be randomised to receive either TEB (standard treatment) or PVB (interventional treatment).

3.2. Trial Setting

Patients under the care of participating surgical and anaesthetic care teams at approximately 20 hospitals. throughout the UK.

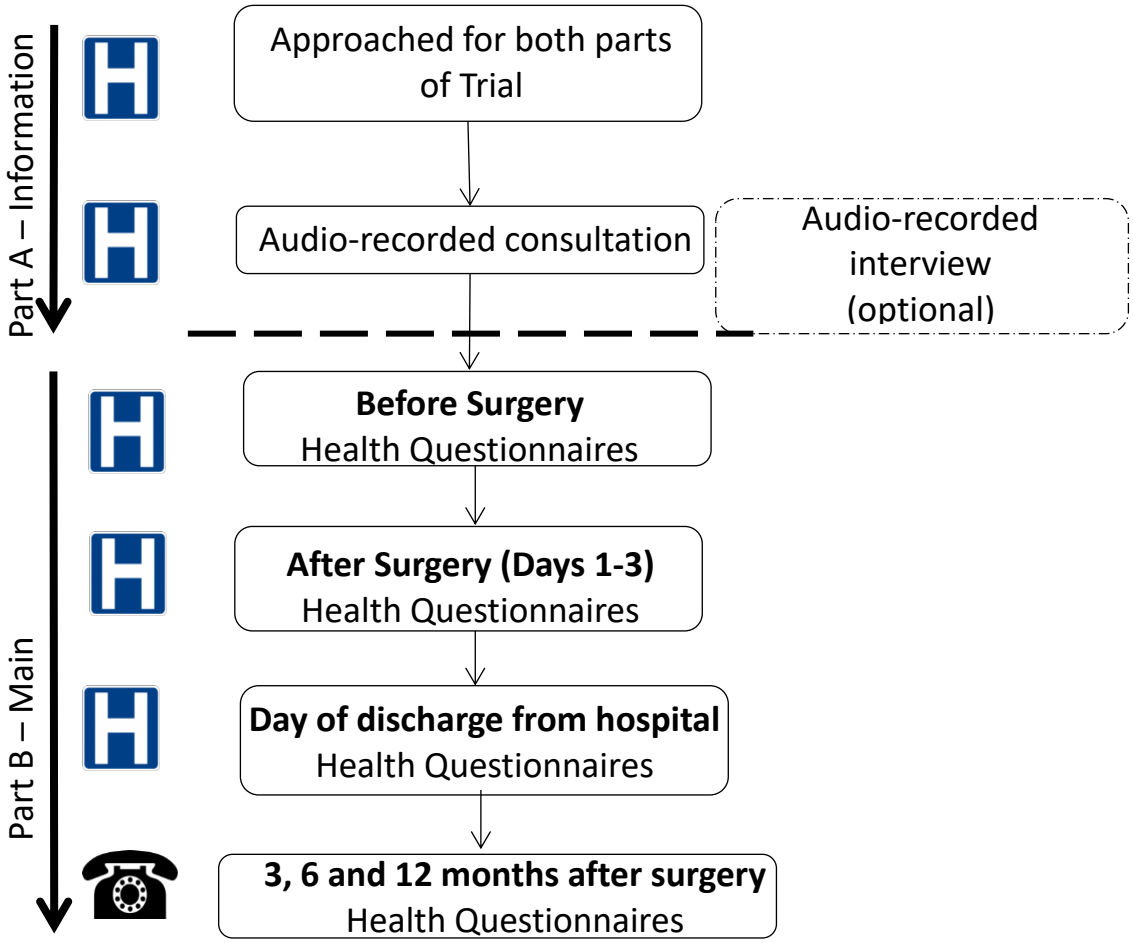
3.3. Identification of participants

Patients will be identified directly from clinical lists of adults undergoing elective open thoracotomies. Patients will be identified from participating surgical centres, in the UK, by members of their normal clinical team. Patients who appear to fulfil the inclusion criteria will

be referred to the research team for confirmation by staff who have been identified on the Site Delegation Log as having this responsibility.

Eligibility will be formally confirmed by the PI, or delegate, at site who has access to, and a full understanding of, the patient's medical history. Once eligibility is confirmed the patient will be approached by a suitably delegated member of the site trial team who will inform them of the trial. This approach may be made in a variety of settings e.g. in surgical clinics, pre-operative clinics, in pre-operative wards or by posting the TOPIC2 Patient Information Sheet to the patient with the TOPIC2 Invitation Letter.

The identification of patients in relation to the main and sub-study is best illustrated via the following patient pathway:



3.4. Sub-studies

The QRI will attempt to identify sources of recruitment difficulties as they occur, and implement generic or bespoke strategies to address these. Recruitment processes will be investigated in depth across a small number of clinical centres (i.e. 3 or 4) in the early phases of recruitment, with reviews of other centres as they open and recruitment proceeds. There will be an attempt to ensure these initial centres are as diverse as possible (e.g. in

terms of patient population, current use of anaesthesia, etc.). Lessons learnt from the QRI will subsequently be applied to other centres, combined with continued investigation of recruitment challenges.

The QRI will proceed in two iterative phases: sources of recruitment difficulties are rapidly investigated in Phase I, informing a mix of generic and tailored interventions to improve recruitment in phase II.

3.4.1. Phase I: understanding recruitment

Phase I aims to understand the **TOPIC 2** recruitment process and how this operates in clinical centres. A multi-faceted, flexible approach will be used to investigate site-specific or wider recruitment obstacles. These will comprise one or more of the following methods of data collection:

a) In-depth interviews: Semi-structured interviews will be undertaken with three groups:

(i) members of the Trial Management Group (TMG)

(ii) clinicians or researchers who are involved in trial recruitment ('recruiters')

(iii) eligible patients who have been approached to take part in the trial.

Interviews with members of the TMG and recruiters will explore their perspectives on the RCT and experiences of recruitment. Key topics explored will include: perspectives on the trial design; views about the evidence on which the trial is based; perceptions of equipoise; perceived barriers and facilitators to recruitment; integration of the trial in clinical centres, and any difficulties in implementing the trial protocol.

Interviews with patients will explore views on the presentation of trial information, understandings of trial processes (e.g. randomisation), and reasons underlying decisions to accept or decline the trial. Patients will be purposefully selected, to build a sample of maximum variation based on the centre/clinic they attend, their final decision about trial participation (i.e. accept or decline), and any other clinical (or non-clinical) characteristics that are deemed to potentially have a bearing on their decisions about trial participation. Some of these characteristics will likely emerge from interviews with clinical professionals. Numbers of interviews for each group of informants will be guided by the concept of 'data saturation' – the need to continue sampling until no new themes emerge. Ideally, each clinical member of the TMG, with responsibility for trial design and a minimum of one person involved in trial recruitment per recruiting centre will be interviewed.

All interviews will be audio recorded on an encrypted device, and take place at a mutually convenient location, in a suitably private and quiet setting. All participants will be offered the option to conduct the interview over the telephone. The University of Bristol's 'lone researcher' safety policies will be upheld for any interviews taking place in non-public settings (e.g. participants' homes).

b) Audio-recording recruitment discussions: Scheduled appointments during which the **TOPIC 2** trial is discussed with patients, including telephone conversations, will be audio-recorded on an encrypted device (and potentially observed by researchers from University of Bristol) with written informed consent. These recordings/observations will be used to explore information provision, recruitment techniques, management of patient treatment preferences, and reasons underlying trial-participation decisions. Recording/observing appointments will also enable comparison of reported and actual recruitment practices for recruiters who have also participated in interviews.

c) Mapping of eligibility and recruitment pathways: Detailed eligibility and recruitment pathways will be compiled for clinical centres, noting the point at which patients receive information about the trial, which members of the clinical team they meet, and the timing and frequency of appointments. Recruitment pathways will be compared with details specified in the trial protocol and pathways from other centres to identify practices that are potentially more or less efficient. The QRI researcher will also work closely with the Birmingham Clinical Trials Unit (BCTU) to compose detailed logs of potential participants as they proceed through screening and eligibility phases. This will help to identify points at which patients do not continue with recruitment to the RCT, thus indicating aspects of the recruitment process that may warrant further investigation and/or intervention.

Logs of eligible and recruited patients will be assembled using simple flow charts and counts to display numbers and percentages of patients at each stage of the eligibility and recruitment processes. These figures will be compared across centres, and considered in relation to estimates specified in the grant application/trial protocol.

d) Observation of TMG and investigator meetings: The QRI researcher will regularly observe TMG meetings to gain an overview of trial conduct and overarching challenges (logistical issues, etc.). These meetings may be audio-recorded, subject to written informed consent.

3.4.2. Phase 2: Development and implementation of recruitment intervention strategies

If recruitment difficulties are evident across the trial or in particular centres, the QRI team will work closely with the TMG/CI to formulate a 'plan of action' that intends to improve recruitment and information provision. The components of this plan will be grounded in the findings from phase 1, and may include generic, centre-specific, or individually-targeted interventions. Generic forms may include 'tips' documents that provide suggestions on how to explain trial design and processes, or changes to trial documentation and trial processes. Supportive feedback is likely to be a core component of the plan of action, with the exact nature and timing of feedback dependent on the issues that arise. Centre-specific feedback may cover institutional barriers, while multi-centre group feedback sessions may address widespread challenges that would benefit from discussion. All group feedback sessions will be aided by displaying anonymised data extracts from interviews and audio-recorded consultations. Individual confidential feedback will also be offered – particularly where recruiters experience specific difficulties, or where there is a need to discuss potentially sensitive issues. Investigator meetings/teleconferences and site visits from the CI/TMG members may also be employed to discuss technical or clinical challenges related to the trial (e.g. discomfort surrounding eligibility criteria).

3.4.3. Iterative nature of Phase I/Phase II

The QRI has been presented as two distinct phases for clarity, although in reality these are likely to overlap. For instance, new avenues of enquiry will emerge throughout the conduct of the QRI (e.g. in feedback meetings), and rigorous monitoring of screening logs before/after interventions may indicate a need for further investigations (phase I) or intervention (phase II).

3.4.4. Evaluating the 'plan of action'

The impact of QRI interventions implemented in phase 2 will be evaluated through mixed approaches, including 'before/after' comparisons (number of recruited patients, eligible patients identified, patients accepting allocation) and investigation of changes in recruiter

practice (through continued analysis of audio-recorded appointments). Semi-structured interviews will be conducted with recruiting staff and TMG members to explore their views on QRI interventions and suggestions for areas that would benefit from continued QRI input.

a) Quantitative evaluation

Information about recruitment plans and targets specified in the trial documentation (protocols/funding application) will be recorded prior to the start of recruitment. This will include:

- The target recruitment figures (ideally for each centre, per month). If a target recruitment line has been provided as a figure (i.e. image), the raw data informing this line should be requested from the TMG or BCTU overseeing the trial. Where possible, the rationale behind these targets should be explored and recorded.
- The planned period of recruitment
- The planned number of centres

Recruitment data will be regularly collected (e.g. at least monthly) throughout the recruitment period. As a minimum, this will include the number of patients randomised per centre, per month. Ideally, the number of patients screened, eligible, and approached will also be routinely collected per centre, per month [38].

The timing of interventions stemming from the QRI should be recorded in the form of day/month/year, with a brief description of the activity. All activities should be recorded, including (but not restricted to):

- Feedback of 'phase 1' findings to the CI and/or TMG, including details of the agreed 'plan of action' (and any subsequent plans for intervention).
- 'Global interventions' (not specific to any particular centre – e.g. 'tips and guidance' documents, changes to PISs, early discussion of findings with the chief investigator)
- 'Centre-specific interventions' (e.g. individual or group feedback within a centre).

b) Qualitative evaluation

Reflective interviews will be conducted with key informants once the collaboration with the QuinteT team is drawing to an end. Key informants will constitute any individuals who have been exposed to QRI interventions or had a role in delivering the QRI. This will likely include the CI, trial manager and recruiters who have received feedback/training. Interviews will take place face to face or over the phone, and be informed by a flexible topic guide informed by previous work in this area [39]. Ideally, interviews will be conducted by an independent member of the QuinteT team who has had no prior direct involvement in the RCT.

3.5. Assessment of Risk

All clinical trials can be considered to involve an element of risk simply by virtue of the operational procedures required and, in accordance with BCTU operating procedures, this trial has been risk assessed, to clarify any risks relating uniquely to this trial. This risk assessment concluded that since both the intervention and comparator arm are already extensively used throughout the UK, that the risk to the patient is no higher than that of standard care.

4. ELIGIBILITY

4.1. Inclusion Criteria

- Aged ≥18 years
- Elective open thoracotomy
- Able to provide written informed consent
- Willingness to complete trial questionnaires out to 12 months post randomisation

4.2. Exclusion Criteria

- Contraindication to TEB or PVB e.g. known allergy to local anaesthetics; infection near the proposed puncture site; coagulation disorders, thoracic spine disorders
- Rib/chest wall resection or planned pleurectomy
- Previous thoracotomy on the same side
- Median sternotomy within 90 days

4.3. Co-enrolment

TOPIC 2 is a pragmatic trial and, as such, co-enrolment is permissible if, in the opinion of the local team, the information presented to the patient will not over-burden them and where it is not explicitly prohibited by the trial into which the participant would be co-enrolled.

Given that during the course of **TOPIC 2** new trials may be starting which could be considered to have a confounding influence on this trial, if the local team are in doubt as to the appropriateness of co-enrolment they should contact the **TOPIC 2 Trial Office** using the contact details provided at the front of this protocol.

5. CONSENT

5.1. Consent processes for the QuinteT Recruitment Intervention

5.1.1. Health care professional and TMG member consent

Recruiting staff and TMG member consent will be obtained through a 'master' consent form that covers all aspects of the QRI. The consent form will set out individual clauses, with the option to select 'Yes' or 'No' for each research activity accordingly. Research nurses or the QuinteT researcher will obtain written consent from all staff. This will be a one-off process to cover consent for all future recordings of appointments, interviews, and observations of TMG/investigator meetings throughout the trial.

5.1.2. Patient consent

***Audio recording/observing recruitment appointments*:**

Patients will be provided with an **Audio-Recording Discussions and Interviews Patient Information Sheet** containing the QRI information and will be asked to consent to the QRI

process *in advance* of being asked for consent to participate in the **TOPIC 2** main trial. Recruiters will check if the patient has any questions about the recording process at the first recruitment appointment, and seek written consent to record the discussion. The participant will be given an adequate time to read the PIS and to discuss their participation with others outside of the site research team. It will be made clear to the patient that participation is voluntary and will not affect their entry into the main trial and they can withdraw their participation in audio recordings and/or interviews at any time. Patients who agree will sign a **Audio-Recording discussions and interviews Consent Form** that seeks permission to record future discussions about the trial in the lead up to the patient making their decision about participation.

A copy of the QRI information sheet and consent form will be given to the participant. In addition, if the participant has given explicit consent, a copy of the signed QRI consent form will be sent to the **TOPIC 2** **Trial Office** at Birmingham Clinical Trials Unit (BCTU) trials team for review.

Interviews: The QRI consent form will include a clause that asks patients if they would be willing to be take part in a future research interview ('Yes' or 'No'). Patients who select 'Yes' may then be approached by the QuinteT researcher.

5.2. Consent Process for the TOPIC 2 Main Trial

It will be the responsibility of the Investigator, or suitably qualified delegate, as identified on the Site Signature and Delegation Log, to obtain written informed consent for each participant prior to performing any trial related procedure.

A separate **TOPIC 2 Participant Information Sheet** (PIS) will be provided to facilitate the discussion about the main trial, Investigators, or delegate(s), will ensure that they adequately explain the aims of the main trial. They will explain the main trial intervention along with the anticipated benefits and potential hazards of taking part in the main trial to the participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial or change their status within the trial at any time. The participant will be given an adequate time to read the PIS and to discuss their participation with others outside of the site research team. If the participant expresses an interest in participating in the trial they will be asked to sign and date the latest version of the main trial ICF. The participant must give explicit consent for members of the research team and or representatives of the sponsor to be given direct access to the participant's medical records.

The Investigator, or delegate(s) as above, will then sign and date the main trial ICF. A copy of this ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the main trial ICF maintained in the ISF. In addition, if the participant has given explicit consent, a copy of the signed main trial ICF will be sent to the **TOPIC 2 Trial Office** at BCTU trials team for review.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussions, the name of the trial, summary of discussion,

version number of the PISs given to participant and version number of ICFs signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial or change their status (see section 8.5) within the trial will remain.

Electronic copies of the PISs and ICFs will be available from the Trials Office and will be printed or photocopied onto the headed paper of the local institution. Details of all participants approached about the trial will be recorded on a **TOPIC 2 Participant Screening/Enrolment Log** and with the participant's prior consent, their General Practitioner (GP) will also be informed that they are taking part in the trial.

6. RECRUITMENT, ENROLMENT AND RANDOMISATION

6.1. Enrolment and Screening

1026 patients meeting the eligibility criteria set out in section 4 will be enrolled.

The potential participant's normal care team will screen the patient for eligibility and information recorded on the **TOPIC2 participant Screening /Enrolment log** accordingly. Before randomising the patient, e.g. at the baseline assessment, a member of the research team will fully complete the **Consent and Randomisation CRF** including the eligibility checklist. The person assessing eligibility must have this responsibility delegated (as detailed on the **TOPIC 2 Site Signature and Delegation Log**) and will sign the **Consent and Randomisation case report form (CRF)** to document the eligibility assessment. The signed randomisation form should be filed in the Investigator Site File (ISF), and a true copy sent to BCTU for central monitoring purposes. All information on the randomisation form is required to randomise the patient.

Details of the trial enrolment will be recorded in the participant's medical notes/electronic patient record. This will include confirmation of eligibility and the date of enrolment into the trial and allocated intervention.

6.2. Randomisation

6.2.1. Randomisation Methodology

Participants will be randomised by computer at the level of the individual in a 1:1 ratio to either TEB or PVB. A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the following variables:

- Gender
- Age <65 years or ≥65 years
- Centre
- Thoracotomy for lung cancer resection or for other indication **NOTE: if patient has suspected lung cancer they should be randomised as thoracotomy for lung cancer resection**

A 'random element' will be included in the minimisation algorithm, so that each participant has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received. Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.2.2. Randomisation Process

After participant eligibility has been confirmed and informed consent has been received, the participant can be randomised into the trial. The patient should ideally be randomised on the day of surgery or the working day prior to surgery. All questions and data items on the Consent and Randomisation Form must be answered before a Trial Number can be given. If data items are missing, randomisation will cease and must start again once the information is available. Only when all eligibility criteria and minimisation data items have been provided will a Trial Number be allocated.

Randomisation will be provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (BCTU) (available at **https://www.trials.bham.ac.uk/TOPIC2**). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the trial as detailed on the **TOPIC 2 Trial Site Signature and Delegation Log**. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access either the randomisation process or trial database using another person's login details. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. A telephone toll-free randomisation service ((0044) 0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days.

6.2.3. Randomisation Records

Following randomisation, a confirmatory e-mail will be sent to the site randomiser, local PI, and local Research Nurse.

Investigators will keep their own trial file log which links participants with their allocated trial number in the **TOPIC 2 Participant Recruitment and Identification Log**. The Investigator must maintain this document, which is **not** for submission to the Trials Office.

The Investigator will also keep and maintain the **TOPIC 2 Participant Screening/ Enrolment Log**. The **TOPIC 2 Participant Recruitment and Identification Log** and **TOPIC 2 Participant Screening/Enrolment Log** should be held in strict confidence.

6.3. Informing Other Parties

If the participant has agreed, the participant's GP should be notified that they are in the **TOPIC 2** Trial, using the **TOPIC 2 GP Letter.**

6.4. Blinding

Due to the nature of the intervention attempts to completely blind clinicians would make processes prohibitively complex and expensive due to innate differences in the mode of action in the two analgesic techniques. There are treatment implications for the patients following their allocated procedure and therefore the research staff and treating clinicians will be aware of the intervention received.

With regard to the patients, the proposed primary outcome of pain rating is subjective in nature and the presence of detection bias is a theoretical possibility. However, there is no reason to suspect that recipients of the randomised interventions have strong pre-conceptions with regard to the relative effectiveness of each analgesic technique. Furthermore, the primary outcome would be collected via questionnaires administered by post or phone, at a time remote from the original operative procedure, which are likely to be resilient to the effects of imperfect concealment. The trial participants will not be informed of the intervention allocation but in the pilot study it was acknowledged that it is difficult to maintain this blind throughout their stay in hospital.

7. TRIAL TREATMENT / INTERVENTION

All trial patients will be anaesthetised by thoracic anaesthetists (consultants or senior thoracic trainees with experience in the techniques). Two online training videos detailing insertion of thoracic epidural and paravertebral blocks have been produced alongside supplementary written step-by-step guides (appendix A and B). The online videos can be accessed using the following link: https://coursecraft.net/courses/z9WY4/splash

All anaesthetists participating in the trial must review either the videos and/or written material and confirm that they are able to perform the techniques. Further training, if required, will be provided by trial-designated trainers at each participating site who can demonstrate and observe performance if required. All training material will be freely available online and will act as a reference for participating anaesthetists and surgeons. Training by participating anaesthetists will be documented in training logs and collated by BCTU.

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 judgement on the best insertion techniques for each patient. These include: insertion using ultrasound or landmark techniques, bupivacaine or levobupivacaine and addition of opiate. This represents real world variation in anaesthetic practices and will not contribute to bias since randomisation will ensure balance across groups by centre. These variations will be captured in the case report form (CRF), as will the choice to use ultrasound guidance or landmark technique and the level at which the injection is inserted.

It will be at the local centre's decision whether and how to use patient-controlled epidural analgesia (PCA) and the details will be collated on the appropriate CRF.

7.1. Intervention(s) and Schedule

Local anaesthetic will be delivered by continuous infusion through an epidural/paravertebral catheter for a minimum of 48 hours (where practicable) in both intervention arms.

7.1.1. Standard group: TEB

Usual practice of TEB, epidural catheter is inserted at the spinal level supplying the skin at the incision site, followed by test dose and a loading dose before the start of surgery. An epidural infusion should be set up for use during the operation and for post-operative use (See Appendix A) for further details).

7.1.2. Intervention group: PVB

Three single injections, at the spinal level supplying the skin at the incision site, will be given before the start of surgery. The PVB catheter will be placed under direct vision by a surgeon/anaesthetist during surgery. A loading dose is given before chest closure followed by continuous paravertebral infusion for post-operative use. (See Appendix B for further details)

7.2. Accountability Procedures

All anaesthetics and analgesia will be taken from standard theatre pharmacy stock. As **TOPIC 2** 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 2** Trial Manager.

8. OUTCOME MEASURES AND TRIAL PROCEDURES

All reasonable attempts should be made to ensure that participants attend scheduled appointments at the appropriate times, but where it is not possible to obtain data, either at all or at the correct time, the TOPIC 2 Trial Office should be notified accordingly. Where necessary appointments and telephone interviews can be rescheduled and data collected, but this should be a mechanism of last resort.

The trial contains an internal pilot, running for 12 months from the first site being opened to recruitment in which the following criteria have been set as a guide as to the feasibility of continuing to full recruitment:

- Recruiting at least 218 patients
- Opening at least 13 sites to recruitment
- At least 70% of sites which are open to accrual successfully recruiting a patient

8.1. Primary Outcome

Presence of CPTP at 6 months post-randomisation. Participants will be asked to indicate their 'worst chest pain over the last week' on a visual analogue scale (VAS; 0-100). Presence will be taken to be a score greater or equal to 40 indicating at least a moderate level of pain.

8.2. Secondary Outcomes

There are a number of secondary outcome measures from the time of randomisation including;

- Complications of regional analgesia (failure of blockade, hypotension (systolic blood pressure (<90mmHg)), inadequate pain relief, low respiratory rate (<10/minute), drowsiness, nausea and vomiting, urinary retention, itching, high block, post-dural puncture headache, vascular puncture, pleural puncture) until discharge from hospital
- Occurrence and severity of surgical complications until discharge from hospital (occurrence as defined by the European Society of Thoracic Surgeons dataset (Appendix C) and severity as defined by the Thoracic Morbidity and Mortality (TMM) classification (Appendix D).
- Post-operative pulmonary complications (PPCs) until discharge from hospital (as defined by SteP COMPAC, Appendix E)
- Critical care admission (levels 2 and 3)
- Mortality (reported for all deaths due to all causes)
- Analgesic use
- Acute pain in the 3 days following surgery, completed by the patient (via VAS; BPI)
- Pain at hospital discharge (via VAS, BPI and SF-MPQ-2)
- Chronic pain (via VAS, BPI and SF-MPQ-2, completed by the participant at 3, 6 and 12 months post randomisation)

- Presence of severe pain at its worst (VAS>=70) in chronic phase at 3, 6 and 12 months
- Presence of at least a moderate level of pain at its worst (VAS>=40) in chronic phase at 3 and 12 months
- Presence of severe pain on average (VAS>=70) in chronic phase at 3, 6 and 12 months
- Presence of at least a moderate level of pain on average (VAS>=40) in chronic phase at 3, 6 and 12 months
- Resource use and cost data (resource use intraoperatively, during and following hospital admission, completed by the Research Team at site and via telephone interviews with the patient following discharge, as appropriate)
- General health-related quality of life (by EQ-5D-5L, completed by the participant at hospital discharge and at 3, 6 and 12 months)
- Mental health state (measured by HADS, completed by the participant at hospital discharge and at 3, 6 and 12 months).
- Patient satisfaction (by Likert scale, completed by the participant at hospital discharge and at 3, 6 and 12 months)
- Serious Adverse Events

Table 1 Data collection tools and corresponding outcomes:

Collection tool	Outcome	Possible responses
Visual Analogue Scale (VAS) [46]	Chronic phase: • Worst chest pain over the last week score • Average chest pain over the last week score Acute phase: • Worst chest pain over the last 24 hours score • Average chest pain over the last 24 hours score	All 0-100 (higher=worse score)
Brief Pain Inventory questionnaire (BPI) [47]	Interference score	0-10 (higher=worse score)
Short Form McGill questionnaire (SF-MPQ-2) [48]	• Continuous pain subscale score • Intermittent pain subscale score • Neuropathic pain subscale score • Affective pain subscale score • Overall score	All 0-10 (higher=worse score)
Generic health related quality of life questionnaire (EQ-5D-5L) [49]	• Index score • Thermometer score	• (-0.59=worst outcome, 1.0=best outcome) • (0-100, higher=better)
Hospital Anxiety and Depression Scale questionnaire (HADS) [50]	• Depression score • Anxiety score	Both 0-21 (lower=better)
Likert Scale to assess satisfaction	• Satisfaction with pain therapy after surgery • Satisfaction with care provided by hospital	Very dissatisfied/ Dissatisfied/ Satisfied/ Very satisfied

The trial-mandated level of pain monitoring is in addition to any routine procedures. During hospital admission patients will need approximately 10-15 minutes to complete the patient booklet on each occasion. At baseline, hospital discharge, 3, 6 and 12 months post randomisation, when the patient is required to complete further data, the time needed increases to approximately 30 minutes for the pain-related data, and a further 15 minutes for the health economic data.

Data on mortality, SAEs and hospital admissions will be collated by the research site staff during secondary care visits. That is to say, patients will not have to specifically attend the hospital to achieve this data; it will be collected as part of the process of being in the secondary care environment. Sites should implement a process to notify the trial team at site when trial patients attend the hospital at whichever department.

Data regarding analgesia use, costs to the participant and societal costs will be obtained via telephone interview (conducted by the local research staff).

In addition some data will be collected concerning the trial intervention itself for quality control purposes.

8.3 Trial Procedures

The following are to be performed at baseline:

- Baseline clinical assessments- ASA grade, height and weight, ECOG, shortness of breath category, smoking status, alcohol consumption (within 28 days of intervention)
- Medical history
- Lung function tests FEV1, FVC, DLCO/TLCO (data can be taken from assessment within past 6 months prior to intervention).
- Valid informed consent
- Patient completed Booklet (within 28 days of intervention)

The following are to be performed on Day 0 (day of intervention):

- Randomisation - The patient should ideally be randomised on the day of surgery or the working day prior to surgery
- Trial intervention – TEB or PVB
- Collect Post-Operative Surgical Complications – these are defined in appendix C.
- Collect Post-Operative Pulmonary Complications – these are defined in appendix E
- Collect Complications of Regional Anaesthesia to include Failure of blockade, hypotension (systolic blood pressure (<90mmHg)), inadequate pain relief, low respiratory rate (<10/minute), drowsiness, nausea and vomiting, urinary retention, itching, high block, post-dural puncture headache, vascular puncture, pleural puncture).
- Collect resource use data
- SAE check

The following are to be performed on Acute day 1, 2, 3 post-surgery and hospital discharge:

NOTE- Day 1 is the first full calendar day (from 12 midnight) post-surgery, day 2 is second full calendar day and day 3 is third full calendar day.

- Collect resource use data
- Collect Post-Operative Surgical Complications – these are defined in appendix C.
- Collect Post-Operative Pulmonary Complications – these are defined in appendix E
- Collect Complications of Regional Anaesthesia to include Failure of blockade, hypotension (systolic blood pressure (<90mmHg)), inadequate pain relief, low respiratory rate (<10/minute), drowsiness, nausea and vomiting, urinary retention,

itching, high block, post-dural puncture headache, vascular puncture, pleural puncture).
- Patient completed booklet - Please note that if patient is discharged prior to day 3 then on the day of discharge they should complete only the hospital discharge patient booklet.
- SAE check

The following are to be performed at 3, 6 and 12 months follow up:

NOTE- follow up time points are from date of randomisation.

- Patient completed booklet
- Collect resource use data, out of pocket costs incurred by participants, societal cost data
- SAE check

8.4 Schedule of Assessments

All timings are taken from date of intervention during the acute phase (up to hospital discharge) then from randomisation

			Acute Phase				Chronic Phase			
Visit	Screening	Baseline	Day 0 (day of intervention)	Day 1 *	Day 2 *	Day 3 *	Hospital Discharge	Month 3	Month 6	Month 12
Eligibility check	x									
Medical History		x								
Baseline Clinical Assessments[1]		x								
Valid informed consent		x								
Randomisation[2]			x							
Lung function tests (FEV1, FVC, DLCO/TLCO)[3]		x								
Trial Intervention			x							
Resource use (analgesics use etc.)			x	x	x	x	x	x	x	x
Mortality Check			x	x	x	x	x	x	x	x
Post-operative surgical complications[4]			x	x	x	x	x			
Post-operative pulmonary complications[5]			x	x	x	x	x			
Complications of regional anaesthesia[6]			x	x	x	x	x			
SAE check			x	x	x	x	x	x	x	x
Out of pocket costs incurred by participants								x	x	x
Societal cost (productivity loss etc.)								x	x	x
Pain questionnaires (VAS, BPI)		x		x	x	x	x	x	x	x
Pain questionnaire (SF-MPQ-2)		x					x	x	x	x
Quality of life questionnaires (EQ-5D-5L and HADS)		x					x	x	x	x
Patient Satisfaction (patient questionnaire)							x	x	x	x

Notes

* Day 1 is first full calendar day (from 12 midnight) post-surgery, day 2 is second full calendar day, day 3 is third full calendar day. Please note that if patient is discharged prior to day 3 then on the day of discharge they should complete only the hospital discharge patient booklet.

[1]To include: ASA grade, Height & Weight, ECOG, Shortness of Breath Category, Smoking Status, Alcohol Consumption. These should be assessed within 28 days of the intervention.

[2]Randomisation should ideally be performed on day of surgery or working day prior to surgery.

[3]Lung function data can be taken from assessment within past 6 months prior to the intervention.

[4]Post-operative surgical complications are defined in Appendix C.

[5]Post-operative pulmonary complications are defined in Appendix E.

[6]To include the following: Failure of blockade, hypotension (systolic blood pressure (<90mmHg)), inadequate pain relief, low respiratory rate (<10/minute), drowsiness, nausea and vomiting, urinary retention, itching, high block, post-dural puncture headache, vascular puncture, pleural puncture.

8.5 Participant Withdrawal

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial (or part of) at any time. The sample size calculation allows for some participant withdrawal, so it is not anticipated that it will be necessary to replace participants who withdraw. The situation will be monitored throughout the trial by the oversight committees, however, and appropriate action may be taken if required.

Types of withdrawal will be collected on a "Change of Status Form" and are defined as below:

- The participant would like to withdraw from trial intervention, but is willing to be followed up in accordance with the schedule of assessments and, using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis). Where a patient is unable to receive the intervention e.g. for technical or resource issues, their data will continue to be collected and analysed in accordance with intention-to-treat.

- The participant would like to withdraw from trial intervention and does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes)

- The participant would like to withdraw from trial intervention and is not willing to be followed up in any way for the purposes of the trial and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis)

The details of withdrawal including date, reason (if provided) and type of withdrawal should be clearly documented in the source data.

If following randomisation the patient does not go on to have a thoracotomy they should be withdrawn from the trial.

9. ADVERSE EVENT REPORTING

9.1. Definitions

Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event		An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: a. Results in death b. Is life-threatening* c. Requires hospitalisation or prolongation of existing hospitalisation d. Results in persistent or significant disability or incapacity e. Consists of a congenital anomaly/ birth defect f. Or is otherwise considered medically significant by the Investigator**
Unexpected and Related Event		An event which meets the definition of both an Unexpected Event and a Related Event
Unexpected Event		The type of event that is not listed in the protocol as an expected occurrence.

* Life threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

9.2. Reporting Requirements

The recording and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments) and the requirements of the Health Research Authority (HRA). Definitions of different types of AEs are listed in section 9.1.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also of causality (relatedness) in relation to the intervention(s) in accordance with the protocol.

9.3. Adverse Events Requiring Reporting in TOPIC 2

The safety profile for this trial population and interventions are well established so a strategy of targeted recording of AEs will therefore not affect the safety of participants. The recording of only the following subset of AEs during the patient's hospital admission via the appropriate CRFs is consistent with aims of the trial.

Postoperative-surgical complications

- Occurrence of post-operative surgical complications will be defined as per the European Society of Thoracic Surgeons (ESTS) database [40] (Appendix C)

Postoperative-pulmonary complications

- This trial will follow the StEP Core Outcome Measures in Perioperative and Anaesthetic Care (COMPAQ) definitions of postoperative pulmonary complications (Appendix E)

Complications of regional anaesthesia

- Failure of blockade, hypotension (systolic blood pressure (<90mmHg)), inadequate pain relief, low respiratory rate (<10/minute), drowsiness, nausea and vomiting, urinary retention, itching, high block, post-dural puncture headache, vascular puncture, pleural puncture).

Severity of the above complications will be classified according to the Seeley Systematic Classification of Morbidity and Mortality After Thoracic Surgery (TM &M) Classification of Severity (Appendix D)

9.4. Serious Adverse Advents (SAE) Reporting in TOPIC 2

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, throughout the participant's time on trial.

9.4.1. Events not requiring reporting to the Sponsor on an SAE form

At whatever time they occur during an individual's participation, from randomisation to end of participant follow-up the following are "protocol exempt" SAEs:

- Pre-planned hospitalisation
- Hospital admissions lasting less than 24 hours

Events of known consequence of the intervention or thoracic surgery, as defined in section 9.8.1, that meet the definition of serious and occur during the patient's post-thoracotomy hospital stay do not need to be reported via an SAE form. As they are of known consequence of either the thoracic surgery or intervention a relatedness assessment is not required and they will be captured in the acute data set.

9.4.2. Events that require reporting to the Sponsor via the SAE Form

The following events should be reported to the trial office immediately and within 24 hours of being made aware of the event:

- All events that meet the definition of serious that occur during the reporting period (see section 9.5) except either those stated in section 9.4.1, or those listed in section 9.8.1 that occur during the post-thoracotomy hospital stay.
- All events that meet the definition of serious and judged to be at least possibly related to the intervention must still be reported irrespective of how long after intervention the event occurred.

Note that when an SAE occurs at the same hospital at which the patient is receiving trial treatment or is being followed up for trial purposes, processes must be in place to make the trial team at the hospital aware of any SAEs, regardless which department first becomes aware of the event, in an expedited manner.

9.5. Reporting period

Details of targeted AEs as described in section 9.3 will be reported during the patient's post-thoracotomy hospital admission. Serious adverse events should be reported from date of intervention until 30 days after the intervention. All events that meet the definition of serious and judged to be at least possibly related to the intervention must still be reported irrespective of how long after intervention the event occurred.

9.6. Reporting procedure

9.6.1. Reporting procedure for Serious Adverse Events by sites

On becoming aware that a participant has experienced an SAE, the Investigator or delegate(s) should report the SAE to their own Trust in accordance with local practice and to the BCTU trials office as per section 9.4 above.

To report an SAE to the BCTU trials office, the Investigator or delegate(s) must complete, date and sign the **TOPIC 2 SAE Form**. The completed form together with any other relevant, appropriately anonymised, data should be faxed, or emailed, to the **TOPIC 2 Trial Office** using one of the numbers listed below within 24 hours of first awareness:

To report an SAE, fax the SAE Form to:

0121 415 9135

Or scan and email the SAE Form to:

TOPIC2@trials.bham.ac.uk

On receipt of an SAE form, the BCTU trial office will allocate each SAE a unique reference number and return this via fax or email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from BCTU or if the SAE has not been assigned a unique SAE identification number within 1 working day, the site should contact the BCTU trial office. The site and the BCTU trial office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the initial SAE report in the Site File.

Where an SAE Form has been completed by someone other than the Investigator, the original SAE form will need to be countersigned by the Investigator to confirm agreement with the causality and severity assessments.

9.6.2. Provision of follow-up information

Following reporting of an SAE for a participant, the participants should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the BCTU trials team.

9.7. Assessment of relatedness

On receipt of an SAE Form the Trials Office will forward it, with the unique reference number, to the CI or delegate(s) who will independently determine the causality of the SAE. An SAE judged by the PI or CI or delegate(s) to have a reasonable causal relationship with the intervention will be regarded as a related SAE. The causality assessment given by the PI or delegate will not be downgraded by the CI or delegate(s). If the CI or delegate(s) disagrees with the PI's (or delegates) causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

When completing an SAE form, the PI or medically qualified delegate will be asked to define the causality and the severity of the SAE. In defining the causality the PI or delegate must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which do not contribute to the event.

Table 2. Relatedness definitions

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

9.8. Assessment of Expectedness

The CI or delegate(s) will also assess all related SAEs, except those stated in section 9.4.1, for expectedness with reference to the following criteria.

Table 3. Expectedness definitions

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in this protocol.
Unexpected	An adverse event that is not consistent with known information about the trial related procedures.

If the event is unexpected, i.e. is not defined in the protocol as an expected event, it will be classified as an Unexpected and Related SAE.

9.8.1. Protocol defined expected AEs

The following events are a known consequence of either intervention:

- failure of blockade
- hypotension
- inadequate pain relief

The following events are a known consequence of paravertebral blockade:

- vascular puncture
- pleural puncture
- pneumothorax

The following events are a known consequence of thoracic epidural block:

- urinary retention
- itching
- inadequate pain relief
- nausea and vomiting
- post-dural puncture headache

Events detailed in appendix C and appendix E are of known consequence of thoracic surgery.

Additionally the following events are also of known consequence of thoracic surgery:

- Prolonged air leak
- Pleural effusion
- Pneumothorax
- Respiratory failure (type 1 and 2)
- Post-surgical bleed
- Bronchopleural fistula
- Surgical emphysema
- Chylothorax

9.9. Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) will provide oversight of the data relating to SAEs at their meetings.

BCTU will report all events categorised as Unexpected and Related SAEs to the main REC, Sponsor and Research Governance Team (RGT) within 15 days.

The main REC and RGT will be notified immediately if a significant safety issue is identified during the course of the trial.

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to PIs. A copy of any such correspondence should be filed in the site file and TMF.

9.10. Urgent Safety Measures

If any urgent safety measures are taken, the BCTU shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the circumstances giving rise to those measures.

9.11. Monitoring pregnancies for potential Serious Adverse Events

There is no identified risk of congenital anomalies or birth defects in the offspring of participants as a result of their participation in the trial.

10. DATA HANDLING AND RECORD KEEPING

10.1. Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

Some data variables may be entered directly onto the CRF, these are clearly identified and detailed below.

Table 4 Source Data Definitions

Data	Source
Patient Reported Data (VAS, BPI, SF-MPQ-2, EQ-5D-5L, HADS, Patient Satisfaction)	The original participant-completed paper form is the source and will be forwarded directly to the **TOPIC 2** Trial Office
Clinical event data	The original clinical annotation is the source data. This may be found on clinical correspondence, or electronic or paper patient records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source data.
Resource use and cost data	During the patient's post-thoracotomy hospital stay the source will be the medical record or CRF (if source data directly documented on CRF) but whether it is the medical record or the CRF should be clear and consistent at any given centre. That is, what constitutes the source should be documented and the same for all patients at that centre . Follow up data will be completed directly on to the CRF via interview with the patient and this will constitute the source data.
Recruitment	The Consent and Randomisation Form is the source.

Attitudes to Recruitment (QRI)	Recordings will be collected by trial staff across the clinical centres, and transferred to and from the University of Bristol through University of Bristol-approved secure data transfer facilities or encrypted flash drives that adhere to NHS Trust policies.
Drop out	Where a participant expressed a wish to withdraw, the conversation must be recorded in the source data.

10.2. Case Report Form (CRF) Completion

A CRF is required and should be completed for each individual subject. The data held on the completed original CRFs are the sole property of the respective PIs whilst the data set as a whole is the property of the Sponsor and should not be made available in any form to third parties except for authorised representatives or appropriate regulatory authorities without written permission from the sponsor.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The **TOPIC 2 Site Signature & Delegation Log** will identify all those personnel with responsibilities for data collection.

The CRFs will comprise the forms in the following table:

Table 5: Data Collection Forms

Form Name	Schedule for submission	Submission Format
Consent and Randomisation Form	Following randomisation	Paper
Consent for QRI	Following consent for QRI	Paper
Baseline Medical Data Form	Following randomisation	Electronic
Patient Completed Booklet Hospital Baseline	Following completion at baseline	Paper
Intervention Form	Following surgery	Electronic
Operation Details Form	If lung cancer indication following receipt of tumour histology results, if other indication following surgery	Electronic
Acute Phase patient completed booklet (Day 1, Day 2, Day 3)	Following acute day 3	Paper
Acute Day 0 Post Recovery Form	Following day of surgery	Electronic

Acute Phase Up To Day 3 Form	Following acute day 3	Electronic
Acute Phase Day 4 to Discharge Form	Following hospital discharge	Electronic
Patient Completed Booklet Hospital Discharge	Following hospital discharge	Paper
Serious Adverse Event Form	Faxed/emailed within 24hrs of research staff at site becoming aware of event.	Paper
Trial Exit/Change of Status Form	At the point of withdrawal or research staff at site becoming aware of death	Electronic
Chronic Phase patient completed booklet (3 month, 6 month, 12 month)	N/A – returned by participant	Paper
Health Contacts Form (3, 6 and 12 months)	Following trial appointment with patient at appropriate time point	Electronic

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs should refer to the **TOPIC 2 CRF completion guidelines**.

For the **TOPIC 2** trial, CRFs will be an electronic record completed at site (except for patient completed booklets and Serious Adverse events which will be paper), only by those at site delegated the task of doing so. Forms will be considered "complete" once all data fields have been either completed unambiguously or it has been made explicit that the data is unobtainable.

In all cases it remains the responsibility of the site's PI (or delegate) to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the site's PI (or delegate) on the CRF.

The local trial team can collate data to be entered onto the electronic database using paper copies of the data forms as worksheets, for simplicity. Where data exists in written form prior to this collation, the original record is the source data. If the data is written directly onto the worksheet, without any previous written record, the worksheet itself becomes the source data. The local team need to have a consistent approach to the use of worksheets so that it is clear if they are to be considered source data or not.

Data should be submitted according to section 10.4 in a timely manner, therefore if data has not been provided within four weeks of the submission schedule detailed in table 5 above then a reminder email will be sent to sites. If the data has still not been received within 6

weeks then the trial manager will directly contact the site via telephone to ascertain the reason for the delay. At 8 weeks from expected submission if the data still has not been received this may be escalated to site's senior management and can trigger a monitoring visit.

10.3. Participant completed Questionnaires

Data collected from participant completed questionnaires forms the basis of the primary outcome. The location of the participant whilst completing the questionnaire will vary according to their individual health situation but generally, during the acute phase, the participant will be in hospital and can complete the forms at any time on the appropriate date. Questionnaires should generally be completed by the participant alone but physical assistance in completing the form can be given by the research staff or the participant's friends and relatives where appropriate. In such circumstances questions are to be read to the participant verbatim and responses must not be led by the person assisting with the form completion. This requirement must be made clear when the participant's friends and relatives are providing the assistance.

Participants should be encouraged to respond to all questions but can refuse to answer any, or all, of the questions should they wish. Where a questionnaire is returned to the local research staff, in person, with some questions unanswered, research staff should clarify with the participant that they have chosen not to respond specifically to the unanswered questions and that they have not simply missed them in error.

During the chronic phase, questionnaires will be posted directly to the participant by the local site with a self-addressed envelope to enable return of the questionnaires directly to the **TOPIC 2** Trial Office.

10.4. Data Management

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan. Coding and validation will be agreed between the trial manager, statistician and programmer and the trial database will be signed off once the implementation of these has been assured.

Missing and ambiguous data will be queried using a Data Clarification system in line with the **TOPIC 2 Data Management Plan**, and will focus on data required for trial outcome analysis and safety reporting. Single data entry with central monitoring will be employed. Staff at site (as delegated on the **TOPIC 2 Site Signature & Delegation Log**) will enter and submit data on an electronic CRF online (except patient completed booklets and serious adverse events) at https://bctu-redcap.bham.ac.uk/. Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of CRF completion as detailed on the **TOPIC 2 Trial Site Signature and Delegation Log**. These unique log-in details must not be shared with other staff and under no circumstances should staff at sites access the trial database using another person's login details. The trial office will be unable to edit data forms entered by site staff. The system will include data validations to improve data quality (e.g. to prevent nonsensical dates or numerical values). Changes to the data on the system will be documented and

attributable, and will be made by local site staff (except for patient completed booklets and serious adverse events).

Patient completed booklets will be posted by the site and patient directly to the trial office and Serous Adverse Event Forms will be emailed or faxed directly to the trial office for trial office staff to enter the data on the electronic CRF online. Site staff will be unable to edit this data.

Trial office staff will perform self-evident corrections if necessary in the following situations:

- to correct general spelling mistakes
- obvious date errors
- where a response to a question has not been provided but additional "related" data has been supplied and where the correct data is recorded on the CRF but in an incorrect location
- Where the trial number is incorrectly recorded on the paper CRF, but the patient can be unequivocally identified from the other patient identifiers on the form, the number may be amended.

TOPIC 2 is a non-CTIMP which has been formally risk assessed by BCTU as "low risk" on the basis that both interventions are already in common usage throughout the UK and the safety profiles are well established. Therefore on-site monitoring will be limited to the first 5 sites to recruit a patient. Source data may be checked against the CRFs where on site monitoring is conducted and must be available for verification.

10.5. Data Security

The security of the System is governed by the policies of the University of Birmingham. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the University of Birmingham have to be registered with the Data Protection Officer and data held in accordance with the Data Protection Act 2018. The University will designate a Data Protection Officer upon registration of the trial. The Trial Centre has arrangements in place for the secure storage and processing of the trial data which comply with the University of Birmingham policies.

The System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls used non-identifiable data etc.
- Network security measures: including site firewalls, antivirus software, separate secure network protected hosting etc.
- System Management: the System shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.

- System Design: the system shall comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within the Trial Centre (University of Birmingham).
- Data processing: Statisticians will have access to anonymised data.
- System Audit: The System shall benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - Periodic IT risk assessments
- Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.
- In addition to the data held for the main trial, source data will be collated for the QRI sub-study by University of Bristol

10.6. Archiving

All records created by following trial procedures, and all documents listed in guidance relating to the conduct of the trial, must be retained and archived including electronic documents, where used. No documents should be destroyed without prior approval from the Trials Office.

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, Pharmacy Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 10 years.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Site Set-up and Initiation

All PIs will be asked to sign the necessary agreements including a Site Signature and Delegation log between the PI and the CTU, and supply a current CV and GCP certificate to BCTU. All site staff who are performing trial specific tasks are required to sign the **Site Signature and Delegation Log**, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either via a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The **TOPIC 2** trials team must be informed immediately of any change in the site research team.

11.2. Monitoring

The monitoring requirements for this trial have been developed following trial specific risk assessment by BCTU.

11.2.1. Onsite Monitoring

For this trial we will monitor the first 5 sites to recruit participants to the main trial within 90 days of randomisation of the first patient at those sites. This is specifically to ensure that the eligibility criteria are being correctly employed and that the trial data is achievable. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, high or low SAE reporting rates, excessive number of participant withdrawals or deviations or any other aspect of the trial conduct that raises concerns with regards to quality management.

Any monitoring activities will be reported to the trials team and any issues noted will be followed up to resolution. If a monitoring visit is required the trial office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the **TOPIC 2** trial staff access to source documents as requested.

11.2.2. Central Monitoring

The trial office will be in regular contact with the site research team to check on progress and address any queries that they may have. The trial office will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent data clarification forms (DCFs) requesting missing data or clarification of inconsistencies or discrepancies.

Sites will be requested to send in copies of signed ICFs and other documentation for in-house review for all participants providing explicit consent. This will be detailed in the **TOPIC 2** Monitoring Plan.

11.3. Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The investigator will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

11.4. Notification of Serious Breaches

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group, Trial Steering Committee, and the REC.

This includes reporting serious breaches of GCP and/or the trial protocol to the REC. A copy is sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC and/or relevant regulatory bodies.

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. Sites are therefore requested to notify the **TOPIC 2** Trials Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

12. END OF TRIAL DEFINITION

The end of trial will be 9 months after the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The BCTU trial team will notify the main REC and RGT within 90 days of the end of trial. Where the trial has terminated early, the Trials Office will inform REC within 15 days of the end of trial. The Trials Office will provide them with a summary of the clinical trial report within 12 months of the end of trial.

A copy of the end of trial notification as well as the summary report will also be sent to the University of Birmingham Research Governance Team at the same time as these will be sent to the REC.

The BCTU trial team will notify the main Research Ethics Committee (REC) and Research Governance Team (RGT) at University of Birmingham that the trial has ended within 90 days of the end of trial and will provide these parties with a summary of the clinical trial report within 12 months of the end of trial.

13. STATISTICAL CONSIDERATIONS

13.1. Sample Size

Assuming a 30% incidence of CPTP in the TEB group (similar to that seen in our previous TOPIC-pilot results [15] and systematic review [6], 392 patients in each group will give 90% power (two-sided p=0.05) to detect a 10% absolute reduction (i.e. down to 20%, a 33% relative reduction) in the PVB group. Assuming a 10% rate of death (similar to that seen in TOPIC) and a further 15% loss to follow-up at 6 months we will recruit 1026 participants.

Our survey of practise of consultant thoracic anaesthetists at UK thoracic centres indicated that a 50% relative reduction in incidence of CPTP would be enough for them to change practice TEB to PVB (or vice-versa). We have powered the trial on a 33% relative reduction

which we think is more realistic and likely to be closer to any minimally important difference [41].

13.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below. The primary comparison groups will be composed of those treated with perioperative paravertebral blockade (PVB) post operation, versus those treated with thoracic epidural blockade (TEB). In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol deviation and excluding patients that did not go on to have surgery. For all outcome measures, appropriate summary statistics will be presented by group (e.g. frequencies and percentages for categorical, mean and standard deviation for continuous). Intervention effects will be adjusted for the minimisation variables listed in section 6.2 where possible. No adjustment for multiple comparisons will be made.

13.2.1. Primary Outcome Measure

The primary outcome is the presence of CPTP at 6 months post randomisation. A mixed effects log-binomial regression model will be used to calculate an adjusted relative risks and 95% confidence intervals, adjusting for the intervention group and the minimisation variables listed in section 6.2. All minimisation variables will be treated as fixed effects, apart from centre which will be included as a random effect. The p-value from the associated chi-squared test will be produced and used to determine statistical significance of the estimated treatment group parameter.

13.2.2. Secondary Outcome Measures

Analysis on the presence of CPTP will also be performed at 3 months and 12 months, while all remaining secondary outcomes will be analysed at each time point, as appropriate. Presence of CPTP and mortality will be analysed in a similar fashion as the primary outcome. Questionnaire responses (VAS, BPI, EQ-5D, HADS and SF-MPQ-2) will be converted to scores and analysed using a mixed linear regression model, adjusting for the intervention group, baseline score (if available) and the minimisation variables listed in section 6.2 (again centre will be included as a random effects variable). An F-test will be used to test the significance of the estimated intervention group parameter (p-value produced). Further supportive analyses be will be carried out on questionnaire responses using a repeated measures [42] (multi-level) model incorporating all recorded scores (baseline and the three post-treatment scores). Parameters allowing for participant, intervention group, time, baseline score and the minimisation variables will be included. A random intercept component will also be included.

Regarding safety, the total number of patients experiencing SAEs will be given by intervention group along with a descriptive table of the events, and statistical significance will be determined by a chi-square test. Standard regression methods will be used to analyse other secondary outcome.

13.2.3. Subgroup Analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see section 6.2), apart from centre. Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup interaction parameter in the statistical model) will be performed prior to any examination of effect estimate within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

13.2.4. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all trial participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. This will consist of simulating the missing responses using a multiple imputation approach. Parameters used to simulate the missing responses will include the minimisation variables, intervention group, previous response at each time point and whether the value is missing to death or other reason. It is not anticipated that the randomised interventions will be associated with number of deaths, i.e. missing due to death is expected to be a random event. Additional sensitivity analysis on the primary outcome will involve varying the VAS thresholds to define CPTP as VAS worst chest pain i) greater than 30, and ii) greater or equal to 70. Full details will be included in the Statistical Analysis Plan.

13.3. Impact of COVID-19

Additional analysis will be taken into consideration to assess the impact of the three phases (Pre, During lock-down, Post lock-down) to understand and assess treatment effects. Details pertaining to the analysis will be presented in the SAP. Furthermore, data analysis will also be presented to the DMC.

13.4. Planned Interim Analysis

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the trial. The committee will meet prior to trial commencement to agree the manner and timing of such analyses but this is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (SAEs) at least at annual intervals. Criteria for stopping or modifying the trial based on this information will be ratified by the DMC. Details of the agreed plan will be written into the Statistical Analysis Plan. Further details of DMC arrangements are given in section 14.5.

13.5. Planned Final Analyses

The primary analysis for the trial will occur once all participants have completed the 12-month assessment and corresponding outcome data has been entered onto the trial

database and validated as being ready for analysis. This analysis will include data items up to and including the 12-month assessment and no further.

13.6. Analysis of QuinteT Recruitment Intervention data

Full or targeted sections of interviews and audio-recorded appointments will be transcribed verbatim by an approved transcription service/transcriber that has signed the necessary confidentiality agreements with the University of Bristol. All transcripts will be edited to ensure anonymity of respondent. Data will be managed using NVivo software and stored on encrypted drives at the University of Bristol, in line with the university's data storage policies.

Interview data will be analysed thematically using constant comparative approaches derived from Grounded Theory methodology [43] Analysis will be led by the member of the QuinteT team employed to deliver the QRI, with a sample of transcripts from each of set of stakeholder interviews double coded by a second member of the team. An initial coding frame will be agreed for each set of interviews and reviewed as it evolves through further data collection and analysis. There will an attempt to search for negative cases in relation to themes, and emerging findings will be regularly discussed in team meetings. Evolving descriptive accounts of emerging findings will be prepared throughout the analytical process.

Audio-recorded recruitment consultations and follow up discussions will be subjected to content, thematic, and novel analytical approaches, including targeted conversation analysis [44] and appointment timing (the 'Q-Qat method') [45]. There will also be a focus on aspects of information provision that are unclear, disrupted, or potentially detrimental to recruitment and/or adherence. Thematic approaches, and techniques to maintain rigour, will be similar to those described above (for interviews). [45] [45] [45] [44] [43] [42] [41] [41]

Notes from observations of appointments and TMG/investigator meetings will be recorded in a detailed log. Key issues/themes from these notes will be considered alongside emerging findings from interviews and audio-recorded appointments.

Findings from the above sources will be brought together and reported in descriptive accounts and summary reports, and presented to the CI and TMG. The content of these reports will focus on key recruitment issues identified, and potential solutions to address these.

13.7 Economic Analysis

In order to assess the costs and benefits of PVB compared with TEB both a within study analysis and a model based economic analysis will be undertaken.

Within study analysis
This component will use the data collected within the trial, and estimates of cost-effectiveness will include the main outcome within the trial, which is CPTP at six months post-randomisation. The main economic analysis will assess cost-effectiveness based on incremental cost per quality adjusted life year (QALY) gained at 6 months post-randomisation, with a secondary analysis of cost per case of CPTP avoided at 6 months. It is planned that further data will be collected at a 12 month follow up. If sufficient data are collected, the analysis will be extended to cover outcomes and resource use at 12 months post-randomisation.

Model-based analysis beyond the end-point of the trial
If the trial shows that PVB is effective in reducing CPTP compared with the current analgesic, it will be necessary to assess the cost-effectiveness of PVB in the longer term, to take into account the impact of chronic pain on an individual's quality of life and productivity. Therefore, if deemed necessary, based on the results of the trial, we will use a decision-analytic model to evaluate the longer-term impacts of the different types of analgesic (for up to five years post-surgery, if data allow). The model development process will use, as a starting point, other models developed for chronic pain [51][52]. Assuming that a Markov model is found to be appropriate, it will be constructed using TreeAge Pro software. This is a widely-used software package ideally suited to the construction and analysis of Markov models. The evidence used in the model will be drawn from the trial, with data on longer term costs and outcomes derived from the literature. If data availability permits, a societal perspective will be adopted, alongside a healthcare perspective.

The uncertainty around key parameter estimates will be modelled by the use of probability distributions to allow a PSA to be undertaken. The choice of distributions will be based upon current best practice in modelling [53]. The aim of the decision-analytic model will be to provide information on the potential longer-term costs and health benefits associated with PVB compared with standard care.

Presentation of results
Cost-effectiveness acceptability curves (CEACs) will be used to show the uncertainty surrounding the cost-effectiveness of the intervention, for a range of thresholds for cost-effectiveness [54]. However, the limitations of the CEAC approach will be spelt out when the results are presented [55]. We will use both deterministic and probabilistic sensitivity analyses to explore the effects of the inherent uncertainty in the parameter estimates on the results. The results of the study will be compared with findings on cost-effectiveness reported in related studies to aid interpretation. The economic evaluation will be conducted and reported in accordance with relevant guidelines [56]. For the longer term model based analyses, discounting will be undertaken to reflect recommendations by NICE.

14. TRIAL ORGANISATIONAL STRUCTURE

14.1. Sponsor

The University of Birmingham is the trial Sponsor.

14.2. Coordinating Centre

BCTU is the Coordinating Centre. Delegation of tasks to the BCTU, from the Sponsor, are documented in the **TOPIC 2 Clinical Trials Task Delegation Log**.

14.3. Trial Management Group

The Trial Management Group (membership detailed in the Administrative Information section above) will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

14.4. Trial Steering Committee

A single Trial Steering Committee (TSC) will be created for the **TOPIC 2** trial and meet face-to-face or via teleconference at least once prior to recruitment of the first patient, then at least annually until full publication of **TOPIC 2**, and as required depending on the needs of the trial office.

Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the TSC will: provide overall oversight of the trial, including the practical aspects of the trial, as well as ensuring that the trial is run in a way which is both safe for the patients and provides appropriate feasibility data to the sponsor and investigators.

14.5. Data Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet at least annually as agreed by the Committee and documented in the Charter. More frequent meetings may be required for a specific reason (e.g. safety phase) and will be recorded in minutes.

The DMC will be scheduled to meet prior to the recruitment of the first patient, in a joint meeting with the TSC, one year after the trial opens to recruitment and then annually thereafter until the trial closes to recruitment.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TMG who will convey the findings of the DMC to the Trial Steering Committee, funders, and/or sponsors as applicable. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The trial will stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community.

14.6. Finance

The National Institute for Health Research (NIHR) is funding this trial. Clinical Research Network (CRN) support will be sought. Excess cost for the trial remains part of NHS costs while trial resources outside routine care and not covered by the CRN will be funded by the trial in the form of per patient payments to a maximum of £300 per patient.

15. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the UK Policy Framework For Health And Social Care Research, 2017, the applicable UK Statutory Instruments, (which include the Data Protection Act 2018) and the Principles of GCP. The protocol will be submitted to and approved by the main REC prior to circulation.

Before any participants are enrolled into the trial, the PI at each site will obtain local R&D approval/assurance. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the BCTU trials team.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

The patient information sheet will provide clear details of the anticipated risks and benefits of taking part in the trial and the trial interventions, and may be modified by the findings from the QRI work.

16. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation and Data Protection Act 2018.

Participants will always be identified using their unique trial identification number, date of birth and initials on the Case Report Form and correspondence between the BCTU.

Additionally, participants will give their explicit consent for the movement of their consent form, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to BCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participants' data and will not disclose information by which participants may be identified to any third party. Representatives of the **TOPIC 2** trial team and sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

QRI interviews and recruitment appointments will be recorded on an encrypted digital recorder which will be locked in a secured cabinet at the University of Bristol. Recordings will be transferred onto a computer as soon as possible after each interview, and stored only in a password protected drive maintained by the University of Bristol. Only the qualitative researchers working on this trial will have access to this drive.

Recordings and transcriptions will be named with a trial-assigned participant number, centre initials, and the date of recording. There will be no participant identifiers in files, databases, or transcripts, which will only be labelled with trial assigned participant numbers. Coding keys matching the name of the participants with their trial participation number will be stored in a password protected spreadsheet, which will be maintained and only accessed by the qualitative researchers. All recordings will be coded and securely transferred to a University of Bristol approved transcription company or transcriber that has signed the required confidentiality agreements. All transcripts will be anonymised upon receipt.

All electronic data files will be saved in a secured computer and to a password protected University of Bristol network space, in accordance with the University of Bristol's data security policies.
All nonessential data will be wiped upon completion of the trial. Essential documents will be kept for up to 25 years, after which they will be deleted and all copies destroyed in accordance with the University of Bristol's secure erasure of data policy.

The anonymised interview data (transcripts only) will be uploaded to a 'controlled access' data repository, subject to individual written informed consent from the participants. This has been fully explained in the information sheet, and requires participants to initial a specific statement on the consent form (if they agree).

17. FINANCIAL AND OTHER COMPETING INTERESTS

The interventions used in **TOPIC 2** are already in standard use in the UK and there are no commercial repercussions on using one intervention in preference to another. Members of the TSC and DMC are required to provide declarations on potential competing interests as

part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

18. INSURANCE AND INDEMNITY

The University of Birmingham has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the participant, responsibility for the care of the participants remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

19. POST-TRIAL CARE

The clinical interventions used in the **TOPIC 2** trial are at a single point in time and cannot be amended in any way once performed. As such, there is no need to provide continuing post-trial care other than that used as standard local practice.

20. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Trial Management Group and authorship will be determined by the trial publication policy.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TSC. Manuscripts must be submitted to the TSC in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of University of Birmingham. Intellectual property rights will be addressed in the NIHR contract and separate agreements between Sponsor and individual sites.

21. ACCESS TO FINAL DATA SET

The **TOPIC 2** protocol will be made publicly available via both the **TOPIC 2** webpage, hosted by BCTU and subsequently published in an appropriate journal, in advance of the final data set.

The final data set itself will only be available to the direct **TOPIC 2** Trial Team, including the TSC, in the first instance. It will also be made available upon formal request when the reason for the request is approved by the TSC.

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23. APPENDICES

Appendix A

TOPIC 2 Thoracic Epidural Blockade Guideline

Peri-operative Utilisation

- Institute full monitoring according to AAGBI guidelines.
- Ultrasound or landmark technique can be used for insertion.
- Catheter insertion should be at the appropriate level for skin incision.
- Following an appropriate test dose, an adequate first dose should be given through epidural catheter (e.g. 3-5 ml of 0.25% levo/bupivacaine). Preservative free opiate can be added (e.g. 2-3 mgs of diamorphine). Further boluses of local anaesthetic should be given if appropriate.
- An infusion should be started and used with epidural catheter (e.g. 0.125% levo/bupivacaine and 4mcg/ml fentanyl at a rate 0.1-0.25 ml/kg/h) before the end of the operation.
- All patients should receive additional analgesia (e.g. intravenous Paracetamol, NSAIDs, opiates) if appropriate.

Post-operative Utilisation

- The patient should be assessed regularly and if they have pain, the rate of the infusion can be changed in order to provide adequate pain-relief or further titrated boluses (e.g. 3-5mls of 0.125% levo/bupivacaine with 4mcg/ml fentanyl) should be given for breakthrough pain. Boluses can be directed and given by clinical team or by patient controlled epidural analgesia.
- All thoracotomy patients should be looked after in an appropriate clinical area with regular monitoring. Epidural should be stepped down to oral/IV analgesics after 48 hours.
- Patients should receive regular oral analgesics such as paracetamol and/or NSAIDS; iv morphine PCA should be available for rescue pain-relief.
- Pain score, motor block, nausea and vomiting, neurological status, physiological parameters and area of anaesthetized chest wall should be regularly assessed. The rate of infusion and administration of top-ups should be given according to local policy.

- 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. If appropriate, vasopressor support for blood pressure should be started according to local policy.

- During the post-operative period, any complications of epidural analgesia should be noted. Advice from the acute pain team and the anaesthetist should be sought if pain control is problematic. Alternative analgesia can be given as per patient requirement.

Appendix B

TOPIC 2 Paravertebal Blockade Guideline

Peri-operative Utilisation

- Institute full monitoring according to AAGBI guidelines.
- Ultrasound or landmark technique can be used in insertion.
- 3 preoperative PVB injections at the appropriate levels for skin incision (e.g. 10-15 ml 0.25% levo/bupivacaine with or without adrenaline (1:200000-400000) for each injection).
- Paravertebral catheter should be inserted under direct vision at the appropriate level as early as convenient. Once the surgical paravertebral catheter is inserted, an adequate bolus should be administered via the catheter (e.g. 10 ml 0.25% levo/bupivacaine). Further boluses of local anaesthetic should be given if appropriate.
- An Infusion should be started before the end of the operation (e.g. 0.125% levo/bupivacaine at 15ml/hr or 0.25% levo/bupivacaine infusion at 10 ml/hour).
- All patients should receive additional analgesia (e.g. intravenous Paracetamol, NSAIDs, opiates) if appropriate.

Post-operative Utilisation

- The patient should be assessed regularly and if they have pain the rate of the infusion can be changed in order to provide adequate pain-relief or further titrated bolus of local anaesthetic (e.g. 3-5mls of 0.25% levo/bupivacaine) can be given for breakthrough pain.
- All thoracotomy patients should be looked after in an appropriate clinical area with regular monitoring. Paravertebral blocks should be stepped down to oral/IV analgesics after 48 hours.
- Patients should be prescribed regular oral analgesics such as paracetamol and/or NSAIDS; iv morphine PCA should be available for rescue pain-relief.
- Pain score, motor block, nausea and vomiting, neurological status, physiological parameters and area of anaesthetized chest wall should be regularly assessed. The rate of infusion and administration of top-ups should be given according to local policy.
- If the blood pressure is persistently low or there any other signs of epidural spread or local anaesthetic toxicity the infusion should be stopped immediately and the patient managed according to local policy.

- During the post-operative period, any complications of paravertebral infusion should be noted. Advice from the acute pain team and the anaesthetist should be sought if pain control is problematic. Alternative analgesia can be given as per patient requirement.

Appendix C – Major cardiopulmonary complications as classified by the European Society of Thoracic Surgeons

ARDS: Adult respiratory distress syndrome defined according to the American---European consensus conference. All of the following criteria should be met:
1. Acute onset
2. Arterial hypoxemia with PaO2/FIO2 ratio lower than 200 (regardless PEEP level)
3. Bilateral infiltrates at chest radiograph or CT scan
4. No clinical evidence of left atrial hypertension or pulmonary artery occlusive pressure <18 mmHg
5. Compatible risk factors

Atrial Arrhythmia: new onset of atrial fibrillation/flutter (AF) requiring medical treatment or cardioversion. Does not include recurrence of AF which had been present preoperatively.

Ventricular Arrhythmia: sustained ventricular tachycardia or ventricular fibrillation that has been clinically documented and treated by ablation therapy, implantable cardioverter defibrillator, permanent pacemaker, pharmacologic treatment or cardioversion.

Bronchoscopy for atelectasis: postoperative atelectasis documented clinically or radiographically that needed bronchoscopy.

Pneumonia: defined according to the last CDC criteria. Two or more serial chest radiographs with at least **one** of the following:

- New or progressive and persistent infiltrate
- Consolidation
- Cavitation

And at least **one** of the following:

- Fever (>38°C or >100.4°F) with no other recognized cause
- Leukopenia (<4000 WBC/mm3) or leukocytosis (>12,000 WBC/mm3)
- For adults >70 years old, altered mental status with no other recognized cause

and at least **two** of the following:

- New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
- New onset or worsening cough, or dyspnea, or tachypnea
- Rales or bronchial breath sounds Worsening gas exchange (e.g. O2 desaturations (e.g., PaO2/FiO2 < 240), increased oxygen requirements, or increased ventilator demand).

Pulmonary embolism: confirmed by V/Q scan, angiogram or CT scan.

DVT: deep venous thrombosis confirmed by Doppler study, contrast study or other study and that required treatment.

Myocardial infarct: evidenced by one of the following criteria:

1. Transmural infarction diagnosed by the appearance of a new Q wave in two or more contiguous leads on ECG.
2. Subendocardial infarction (non Q wave) evidenced by clinical, angiographic electrocardiographic signs.
3. Laboratory isoenzyme evidence of myocardial necrosis.

Renal failure: defined as the onset of new renal failure in the postoperative period according to one of the following criteria:

1. Increase of serum creatinine to greater than 2.0, and 2-fold the preoperative creatinine level.
2. A new requirement for dialysis postoperatively.

Neurological complication: occurrence of one of the following central neurologic postoperative events not present preoperatively:

1. A central neurologic deficit persisting postoperatively for more than 72 hours
2. A transient neurologic deficit (transient ischemic attack or reversible ischemic neurological deficit) with recovery within 72 hours
3. A new postoperative coma persisting at least 24 hours and caused by anoxic/ischemic and/or metabolic encephalopathy, thromboembolic event or cerebral bleed.

Appendix D – Seeley Systematic Classification of Morbidity and Mortality After Thoracic Surgery (TM &M) Classification of Severity

Complication: Any deviation from the normal postoperative course.

Minor	
Grade I	Any complication without need for pharmacologic treatment or other intervention.
Grade II	Any complication that requires pharmacologic treatment or minor intervention only.
Major	
Grade III	Any complication that requires surgical, radiologic, endoscopic intervention, or multi-therapy.
Grade IIIa	Intervention does not require general anaesthesia.
Grade IIIb	Intervention requires general anaesthesia.
Grade IV	Any complication requiring intensive care unit management and life support.
Grade IVa	Single organ dysfunction.
Grade IVb	Multi-organ dysfunction.
Mortality	
Grade V	Any complication leading to the death of the patient.

Appendix E – StEP Core Outcome Measures in Perioperative and Anaesthetic Care (COMPAQ) – Post-operative Pulmonary Complications

ARDS - Berlin definition

Timing: within 1 week of a known clinical insult or new or worsening respiratory symptoms **AND**…

Chest imaging: bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules **AND**…

Origin of oedema: respiratory failure not fully explained by cardiac failure or fluid overload (requires objective assessment, e.g. echocardiography, to exclude hydrostatic oedema), **AND**…

Oxygenation: mild PaO_2:FiO_2 between 26.7 and 40.0 kPa (200-300 mm Hg) with PEEP or CPAP_5 cm H_2O; moderate PaO_2:FiO_2 between 13.3 and 26.6 kPa (100-200 mm Hg) with PEEP_5 cmH_2O; severe PaO_2:FiO_2_13.3 kPa (100 mm Hg) with PEEP_5 cm H_2O.

Mechanical ventilation
The need for need for tracheal re-intubation and mechanical ventilation after extubation, and within 30 days after surgery OR mechanical ventilation for more than 24 h after surgery. The inclusion of non-invasive ventilation may be considered on a study by study basis.

Post-operative Complications*

Composite of respiratory diagnoses that share common pathophysiological mechanisms including pulmonary collapse and airway contamination:

(i) atelectasis detected on computed tomography or chest radiograph,
(ii) pneumonia using US Centers for Disease Control
criteria,
(iii) Acute Respiratory Distress Syndrome using Berlin
consensus definition,
(iv) pulmonary aspiration (clear clinical history **AND** radiological evidence).

*Exclusions
Other diagnoses that do not share a common biological mechanism are best evaluated separately and only when clearly relevant to the treatment under investigation:

(i) pulmonary embolism,
(ii) pleural effusion,
(iii) cardiogenic pulmonary oedema,
(iv) pneumothorax,
(v) bronchospasm.

Post-operative Pneumonia

Two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease):
(i) New or progressive and persistent infiltrates, (ii) consolidation
(iii) cavitation; **AND** at least **one** of the following:

(a) fever (>38°C) with no other recognised cause,
(b) leucopaenia (white cell count <4_10^9 litre_1) or leucocytosis (white cell count >12_10^9 litre_1),
c) for adults >70 yr old, altered mental status with no other recognised cause;

AND at least **two** of the following:

(a) new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements,
(b) new onset or worsening cough, or dyspnoea, or tachypnoea,
(c) rales or bronchial breath sounds,
(d) worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand).