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Synopsis

The clinical and cost-effectiveness of paravertebral blockade versus thoracic epidural blockade in reducing chronic post-thoracotomy pain: TOPIC2 RCT synopsis

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Abstract

Background: More than a third of patients undergoing thoracotomy suffer from debilitating chronic post-thoracotomy pain lasting months or years postoperatively. Aggressive management of acute pain during the perioperative period may mitigate this risk.

Objective(s): To determine the clinical and cost-effectiveness of paravertebral blockade compared to thoracic epidural blockade, by testing the hypothesis that paravertebral blockade reduces the incidence of chronic post-thoracotomy pain.

Design and methods: A parallel, open, multicentre, randomised controlled with integrated health-economic evaluation and an internal pilot that incorporated a qualitative recruitment intervention.

Setting and participants: Adult patients undergoing thoracotomy in 15 United Kingdom centres.

Interventions: Paravertebral blockade compared to thoracic epidural blockade.

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Main outcome measures: The primary outcome was the presence of chronic post-thoracotomy pain at 6 months post randomisation defined as 'worst chest pain over the last week' of at least moderate intensity, with a visual analogue scale score ≥ 40 mm. Secondary outcomes included visual analogue scale pain scores in the acute (days 1, 2, 3 and discharge) and chronic (3, 6 and 12 months) phases postoperatively; Brief Pain Inventory; Short Form McGill Pain Questionnaire 2; Hospital Anxiety and Depression Scale; patient satisfaction; analgesia use in the acute and chronic phases; complications (analgesic, surgical and pulmonary) and mortality. For the economic evaluation, the EuroQol-5 Dimensions, five-level version questionnaire was utilised.
Results: Between 8 January 2019 and 29 September 2023, 770 patients underwent randomisation; 33 did not proceed to thoracotomy. At 6 months, 59 (22%) of 272 participants in the paravertebral blockade group and 47 (16%) of 292 in the thoracic epidural blockade group developed chronic pain [adjusted risk ratio = 1.32 (95% confidence interval 0.93 to 1.86); adjusted risk difference = 0.05 (95% confidence interval −0.01 to 0.11); $p = 0.12$]. During the acute phase, both worst and average pain was higher on day 1 with paravertebral blockade [adjusted mean difference 7.7 mm (95% confidence interval 2.8 to 12.5) and 7.0 mm (95% confidence interval 2.7 to 11.2), respectively] but not different on days 2 and 3. Hypotension was less common in the paravertebral blockade group [adjusted risk ratio = 0.66 (95% confidence interval 0.46 to 0.94)], and overall complications were comparable between groups. The health-economic analysis demonstrated that thoracic epidural blockade produced an additional 0.04 quality-adjusted life-years when compared to paravertebral blockade, and was associated with slightly lower costs, but these differences were not statistically significant.
Limitations: The main limitation is the reduced sample size from 1026 to 770, which reduced the associated power from 90% to 80%. The key reasons are related to practice change over time resulting in a downgrade in equipoise and the COVID pandemic. Also, we cannot rule out that lack of blinding may have had some impact on the acute phase outcomes.
Conclusions: In our study, paravertebral blockade and thoracic epidural blockade appear to be equivalent in clinical and cost-effectiveness in preventing chronic post-thoracotomy at 6 months; this may be paving the way for both techniques likely to continue in National Health Service thoracic settings, based on clinician and patient's choices.
Future work: Using full TOPIC-2 data sets, defined according to the European Society of Thoracic Surgeons data set, to explore the trajectory of the development from acute to chronic post-surgery pain.
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Introduction

Rationale for research and background

Thoracotomy surgery is considered one of the most painful surgical procedures and can cause chronic post-surgical pain lasting months to years postoperatively. The presence of chronic post-thoracotomy pain (CPTP), defined as pain that recurs or persists at least 3 months following surgery,[1] has been reported to occur with an incidence as high as 50%.[2] CPTP can be severe and debilitating to patients, leading to wide-ranging impacts on functional activity and quality of life, more frequent general practitioner visits, anxiety, depression, time off sick and unemployment.[3–5] The well-recognised burden of chronic pain following surgery is such that, '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 professional and patients/carer stakeholder organisations. Clinicians and researchers therefore have a moral and scientific duty to investigate treatments to prevent or reduce chronic post-surgery pain.

Aggressive management of acute pain resulting from thoracotomy may reduce the likelihood of developing chronic pain.[6] Two main analgesic techniques are commonly used for postoperative pain control following thoracotomy, thoracic epidural blockade (TEB) and paravertebral blockade (PVB), both of which seek to block afferent nociceptive transmission at a spinal cord level preventing ascending transmission. Some suggest that by unilaterally blocking afferent nerve transmission at the paravertebral space, PVB could be uniquely effective in preventing long-term pain.[7–9] In our pilot feasibility trial conducted in preparation for presented study, the incidence of CPTP 6 months postoperatively was lower with PVB compared with TEB, but a definitive trial was required to confirm this finding reliably.[10]

For over two decades, both TEB and PVB have been widely used internationally[11–13] for the prevention of acute postoperative pain following thoracotomy with systematic reviews and meta-analyses supporting the use of either technique.[14–18] While there is good evidence that PVB provides equivalent analgesia to TEB for acute pain,[6,14–18] their comparative effects on chronic pain and their relative

health-economic value are unknown. Our Cochrane review of 14 studies (698 participants) comparing the 2 techniques was forced to conclude that there were insufficient data to allow a comparison for these end points.[14]

Objectives

The TOPIC-2 trial was designed to test the hypothesis that in adult patients undergoing elective thoracotomy, the use of PVB for perioperative pain relief reduces the incidence of CPTP at 6 months post randomisation by at least 10% compared with TEB.

Secondary objectives consisted of:

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

In addition, during the first year, the trial was supported by an integrated QuinteT (Qualitative Research Integrated into Trials) Recruitment Intervention (QRI) with the aim of optimising recruitment and informed consent.[19]

This synopsis summarises our previously published work (see *Additional Information*).

Methods for data collection and analysis

Prior to TOPIC-2, a pilot study to assess the feasibility of a trial comparing the two proposed interventions was conducted ('TOPIC-1').[10] Two thoracic centres took part. The key indicators of feasibility relating to the ability to randomise and obtain follow-up data up to 6 months were successfully met, suggesting we should proceed with a substantive trial.

Trial design

TOPIC-2 was a multicentre, open, parallel-group, randomised controlled trial (RCT) with integrated health-economic evaluation and an internal pilot that incorporated a QRI.

The detailed trial protocol has been previously published[20] and the final full trial protocol is provided in the *Additional Information* section. The original research pathway flow diagram can be found in *Figure 1*. The trial aimed to recruit 1026 participants undergoing elective thoracotomy. This target was later reduced to 770 participants.

Participants

Participants were recruited under the care of participating surgical and anaesthetic care teams in 15 thoracic surgical centres throughout the UK.

Inclusion criteria were as follows:

- aged ≥ 18 years
- elective open thoracotomy
- able to provide written informed consent
- willingness to complete trial questionnaires out to 12 months post randomisation.

The exclusion criteria were:

- contraindication to TEB or PVB, for example 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.

Outcomes

Primary outcome

Presence of CPTP at 6 months post randomisation. Participants were asked to indicate their 'worst chest pain over the last week' on a 100-mm visual analogue scale (VAS; 0–100). The presence of CPTP was defined as a VAS score ≥ 40 mm indicating at least a moderate level of pain.[21]

Secondary outcomes

Secondary outcomes consisted of: both worst and average chest pain VAS scores in the acute (days 1, 2, 3 and discharge) and chronic (3, 6 and 12 months) phases postoperatively; Brief Pain Inventory (BPI)[22] in the acute and chronic phases; Short Form McGill Pain Questionnaire 2 (SF-MPQ-2)[23] at discharge and in the chronic phase; health-related quality of life [EuroQol-5 Dimensions, five-level version (EQ-5D-5L)];[24] Hospital Anxiety and Depression Scale[25] at discharge and in the chronic phase; patient satisfaction with pain therapy post-surgery/care provided by hospital (Likert scale); analgesia use in the acute phase and long-term medication use; and complications (analgesic, surgical and pulmonary), critical care admission, mortality and serious adverse events.

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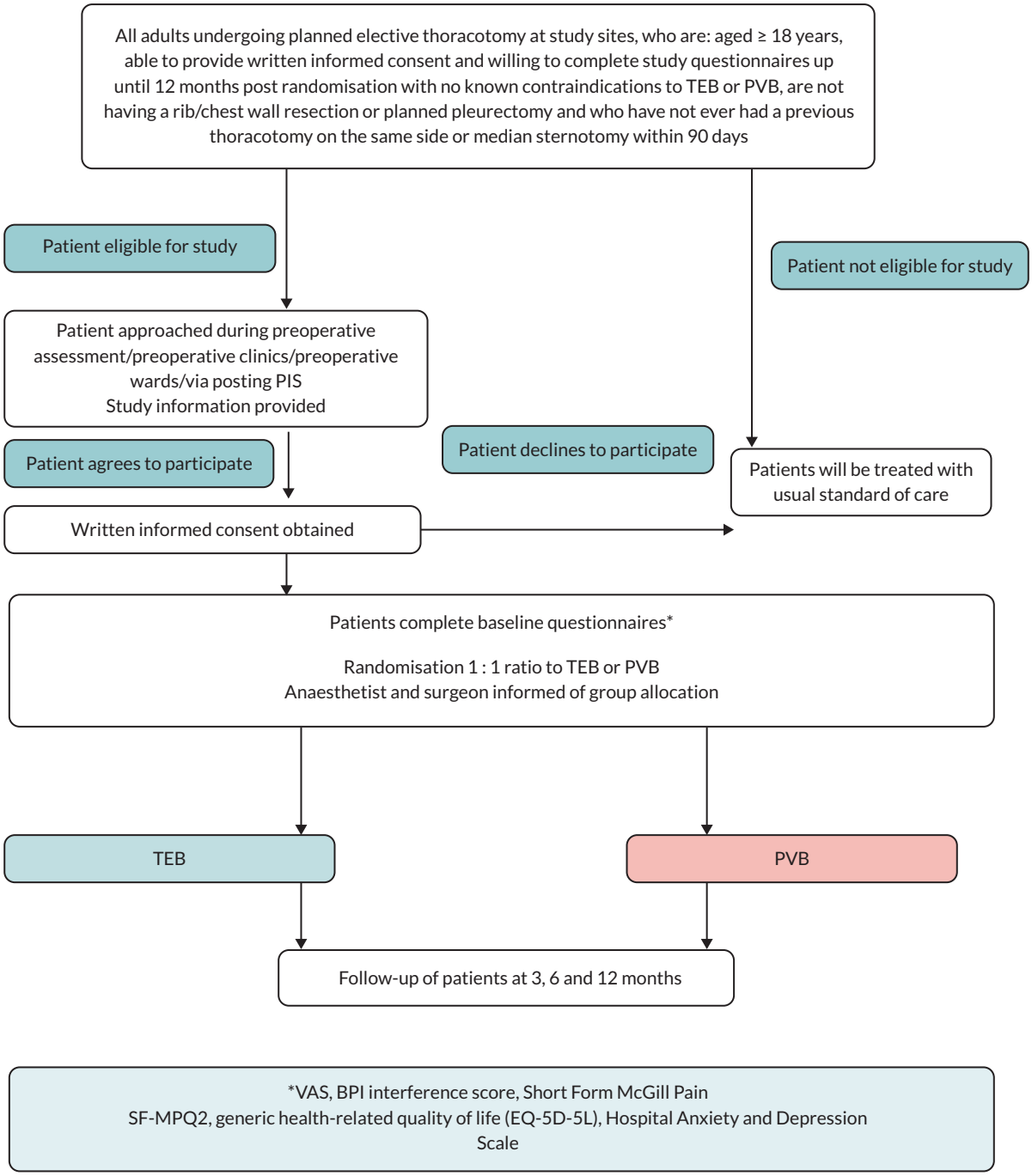

FIGURE 1 Planned research pathway. PIS, patient information sheet.

Randomisation and treatment allocation

Participants were randomly assigned (1 : 1) to receive TEB or PVB through a secure online central randomisation system provided by the Birmingham Clinical Trials Unit, with the use of a minimisation algorithm to balance trial-group assignments according to gender, age (< 65 or ≥ 65 years), operation indication (lung cancer or other) and by recruiting centre.

Interventions

Full details on the trial interventions, including the post-operative analgesic delivery, are provided in the protocol and clinical results paper. In brief, PVB delivery consisted of three single-shot injections, at an appropriate spinal level supplying the skin over the incision site before the start of surgery. A catheter was then subsequently placed under direct vision during surgery, with a loading dose of local anaesthetic given before chest closure followed by continuous paravertebral infusion for postoperative use. For TEB, an epidural catheter was inserted at the spinal level supplying the skin at the incision site, followed by a test and loading dose of local anaesthetic before the start of surgery. An epidural infusion was set up for use during the operation and for postoperative use.

Sample size

The sample size assumed a 30% incidence of CPTP in the TEB group, based on data observed in a systematic review[15] and our pilot study.[10] To detect a plausible 10% absolute reduction (i.e. down to 20%) in the PVB group with 90% power (two-sided alpha of 0.05) required 392 participants per group. Assuming a 10% rate of death by 6-month follow-up and a further 15% loss to follow-up, we aimed to recruit a total of 1026 participants. However, in response to a slower than expected rate of recruitment to the trial, this target was revised to 770 participants in August 2023. This revised sample size used the same assumptions as the initial calculation but had a reduced power from 90% to 80%.

Analysis

In brief, analyses were carried out in a modified intention-to-treat (ITT) population (all participants randomised where a thoracotomy took place). Analysis was carried out using suitable regression models, dependent on data type. All estimates of differences between groups were presented with 95%, two-sided confidence intervals (CIs), adjusting for the minimisation variables where possible (all fixed effects apart from centre which was a random effect).

The primary outcome was analysed using generalised estimating equations to estimate the risk difference and relative risk, incorporating all time points in the chronic phase. A time by treatment interaction term was included to account for any temporal effects in the data. Secondary outcomes of a similar nature (repeated binary measures) were analysed in the same fashion.

For secondary outcomes that were measured continuously and repeated over several time points, adjusted mean differences were produced from mixed repeated-measures linear regression models. Ordered categories were analysed using a generalised estimating equation model with alternating logistic regression including all time points to estimate a common odds ratio and 95% CI. Sensitivity analyses included a per-protocol analysis including only participants who received their randomised intervention were carried out along with a tipping point analysis on the missing primary outcome data to explore if the data could be missing not at random.

Health-economic evaluation

The economic evaluation utilised the data collected within the clinical trial. The main economic analysis aimed to assess cost-effectiveness based on incremental cost per quality-adjusted life-year (QALY) gained at 12 months post randomisation, with a secondary analysis of cost per case of CPTP avoided at 6 months. The primary economic analysis was conducted from a NHS and Personal Social Services perspective, based on cost per additional QALY gained. The methods used for this within-trial analysis were guided by UK National Institute for Health and Care Excellence (NICE) recommendations,[26] and findings were reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards guidelines.[27] All analyses were conducted using Stata 18 (StataCorp LP, College Station, TX, USA). The time horizon for the economic analysis was 12 months; therefore, costs and outcomes were not discounted. All costs are shown in Great British pounds (2021–2).

Resource use and costs

Resource-use data were collected using case report forms, completed by the trial staff until primary hospital discharge, and by the patients at 3, 6 and 12 months. Resource-use data included: (1) the randomised analgesic intervention (PVB or TEB); (2) thoracotomy or the surgical procedure; (3) management in the acute phase, including postoperative management of the local anaesthetic block, analgesia, ward care, critical care and any additional theatre visits; (4) primary care and community-based services, including contacts with primary and community healthcare personnel (general practitioner, practice nurse, physiotherapist, psychologist, counsellor, pain specialist, district nurse, acupuncturist, osteopath, chiropractor and other healthcare contacts); (5) inpatient hospital admissions (re-admissions), including theatre visits; (6) emergency department visits; (7) medications; (8) equipment; and (9) other miscellaneous expenses, such as productivity costs incurred by the patients, as well as any private costs. Private health costs incurred by patients and productivity costs were considered in the sensitivity analysis.

Unit costs were obtained from different sources, including Personal Social Services Research Unit costs,[28] NHS Reference Costs,[29] *British National Formulary*,[30] NHS tariff book[31] and online sources, and Annual Survey of Hours and Earnings.[32] The micro-costing approach was employed to estimate the total costs for different cost categories by multiplying the resource item by the unit cost and summing all the items. All resource use was valued in monetary terms using appropriate UK unit costs estimated at the time of analysis. All costs were valued in Great British pounds for 2021–2.

Health outcomes

The outcome measure for the main economic analysis, a cost–utility analysis was QALYs. In line with NICE recommendations, health-related quality of life was measured using the EQ-5D-5L instrument.[24] The EuroQol-5 Dimensions instrument is a preference-based

measure consisting of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D-5L instrument is widely used and is validated for patients with chronic pain (e.g. Obradovic *et al.*[33]). Each patient's health status descriptions obtained from the EQ-5D-5L were translated into a single, preference-based (utility) index using a UK-specific value set.[34] Following NICE guidance, utility values were calculated by mapping the 5L descriptive system data onto the 3L value set. We used the mapping function developed by van Hout *et al.* for the analysis, to allow consistency with NICE recommendations.[35] This mapping function uses data obtained from a survey of the UK population to derive a utility-based value.[36] Following the trapezium rule, the generated score was used to calculate QALYs gained at different time points from baseline to 12 months after randomisation.[37]

Base-case analysis

For the base-case analysis, both a cost–utility analysis and a cost-effectiveness analysis were planned, with incremental cost-effectiveness ratios (ICERs) estimated where appropriate. The analysis was conducted on an ITT basis, following a pre-agreed health economics analysis plan. Cost and outcome data were summarised and reported as mean values and standard deviations (SDs), and resource use data were reported as medians and interquartile ranges. Given that cost data are likely to be positively skewed, 95% CIs around differences in costs and outcomes from 1000 resamples were measured using the bias-corrected bootstrap method.[38]

Incremental cost-effectiveness ratios were calculated based on the cost per QALY gained. The findings were interpreted using NICE's willingness-to-pay thresholds where an intervention is usually considered as cost-effective if the generated ICER is < £20,000–30,000 per QALY gained.[38]

Sensitivity analyses

A number of deterministic sensitivity analyses were carried out to assess the impact of variation in the estimated values and assumptions on the base case results. To allow consideration of a broader perspective, costs incurred by participants and their families were included in the sensitivity analysis. This included private health costs incurred by patients and productivity costs. To account for uncertainty due to sampling, a probabilistic sensitivity analyses comprising a non-parametric bootstrapping approach was applied to the patient-level data to derive 5000 paired estimates of mean differences in costs and health outcomes.[39] The paired estimates were presented as scatterplots for the cost–utility analyses on a cost-effectiveness plane to facilitate the interpretation.[40]

Qualitative recruitment initiative

The QRI is a complex intervention, which utilises a range of predominantly qualitative research methods to identify barriers to recruitment to a RCT. Following analysis of these barriers, recommendations for strategies to mitigate the barriers are presented to the Trial Management Group (TMG) who may choose how (if at all) to adopt these strategies.

Methods of data collection

The QRI interprets screening and recruitment data informed by the screened, eligible, approached, randomised framework.[41] Interview data are collected from members of the TMG, stakeholders involved in the recruitment of patients to the study, and from clinical representatives from sites that had initially considered participation in the study but ultimately declined to take part. Study sites are asked to take an audio recorder and, with consent, record consultations with eligible patients where the study was discussed.

Screening log reviews

Screening and recruitment data were reviewed monthly throughout the first year of trial recruitment. Two main observations came from this review. Firstly, it was identified that in this time frame, while most centres were recruiting to the approximate target of 2 patients per month, fewer than expected recruiting centres had opened the study (9 compared to a target of 13). Hence, it was decided to approach and interview representatives from sites who had been approached for the study but had either declined or asked to delay their decision to participate.

Secondly, as the recruitment rate for TOPIC-2 was relatively high (at the time of the QRI approximately 67% of eligible patients approached were randomised), it was unlikely that increases in the recruitment rate would fill the shortfall between actual and the target recruitment. Hence, seeking to increase the volume of TOPIC-2 referrals was therefore considered as a key facilitator to increase recruitment.

Interviews

Representatives from all sites open to recruitment at the time of the QRI were invited to participate in a one-to-one interview, as well as all sites who had declined participation. Interviews were undertaken with 13 clinicians from 8 participating sites, including anaesthetists, surgeons,

research nurses and a research practitioner. Three of the interviewees were members of the study TMG. Additionally, interviews were undertaken with seven anaesthetists from seven separate declining sites.

Most anaesthetist interviewees reported a reduction in the number of thoracotomies taking place. Other findings from interviews included that surgeons would play a vital role in recruitment to TOPIC-2. However, it was seen that at some centres, not all surgeons were identifying and referring potentially eligible patients. To mitigate for this, we sought strategies to increase awareness and support for TOPIC-2 among surgeons. The QRI team suggested producing a laminated copy of a 'surgeon a *cue card*' providing simple wording about the study to encourage surgeons to introduce TOPIC-2 to patients.

Across their interviews, we found that research nurses had different approaches to identifying patients locally. In some cases, they screened theatre lists and flagged these to surgeons as potentially eligible patients, whereas others relied on surgeon referrals. Given that we had identified a shortfall in surgeons identifying potentially eligible patients, we recommended that research nurses at all sites should aim to approach all patients (ambiguously listed) for video-assisted thoracoscopic surgery (VATS) ± thoracotomy, to enter these patients onto the screening log, and to speak to surgeons locally about individual cases, to verify what type of operation patients were having in advance such that patients can be approached for TOPIC-2.

Interviewees from declining sites reported how they had fully explored taking part in TOPIC-2 as a clinical team and come to a firm conclusion to decline to participate. Respondents from four sites stated that this was a final decision, and that there is no appetite to reconsider participation. Others were willing to reconsider subject to progress made in pilot/other sites but felt it unlikely that they would participate given the need to change their local practices in order to do so.

Each of the interviewees was asked whether they would be happy to consider both of the analgesic techniques used in TOPIC-2. Many sites had a strong preference to use a PVB and were not willing to consider TEB. Commonly, this preference came from a belief that PVBs were 'as good' as epidurals in terms of pain relief, but also a 'safer' approach. Two site representatives reported that epidurals were so rarely the chosen pain relief method they felt 'deskilled' and hence unwilling to consider performing a TEB. Three sites were concerned about the potential impact of epidurals on intensive care unit (ICU) bed space. They felt that patients receiving a TEB would require a longer hospital stay than those with a PVB and local issues with ICU capacity would make this problematic.

Conversely, the representative from one site stated that they believed epidurals were the 'gold standard' of care and this, combined with their lack of experience of PVBs, made them less confident in undertaking this approach. While this site was an outlier in terms of their preference, they were equally lacking in equipoise for the study design and thus unwilling to take part.

In addition to local pain relief preferences, a minority of site representatives also gave research-related reasons for non-participation. Some stated they were relatively small units with limited research nurse support or research nurses at capacity.

Audio-recorded consultations

Audio recordings were made of 16 TOPIC-2 patient discussions from 5 recruiting centres. Of these patients, 11 consented to be randomised, 2 declined and for the remaining 3 the recording ends with them asking to take further time to make their decision. Examples of good recruitment practices were identified in these recordings and shared with other recruiters through recruitment training and tips.

Recruitment support activities

In addition to providing feedback to regular TMG meetings, the QRI team undertook a range of formal feedback activities based on analysis of TOPIC-2 data and/or informed by prior QuinteT work.

Results summary

Randomised controlled trial

For the primary outcome, the number of participants with CPTP at 6 months was slightly higher in the PVB group, but this difference was not statistically significant [59/272 (22%) vs. 47/292 (16%); adjusted RR 1.32 (95% CI 0.93 to 1.86); adjusted RR 0.05 (95% CI −0.01 to 0.11); $p = 0.12$]. Supportive analyses did not materially alter this finding, although we could not completely rule out some missing responses having some influence, albeit in the direction favouring TEB.

During the chronic phase, most of the patient-reported pain and quality of life secondary outcomes favoured TEB on average, but differences were generally small, not statistically significant and inconsistent over the time frame observed. Analgesic use was similar over 12 months.

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During the acute phase, both worst and average pain as measured by VAS was higher on day 1 with PVB [adjusted mean difference 7.7 mm (95% CI 2.8 to 12.5), 7.0 mm (95% CI 2.7 to 11.2) respectively]; the BPI pain interference score showed similar results on day 1 [adjusted mean difference 0.63 points (95% CI 0.21 to 1.05)]. However, there were no differences in pain as measured by VAS, nor BPI on postoperative days 2–3.

With respect to complications, hypotension [RR 0.66 (95% CI 0.46 to 0.94)] and pruritus [RR 0.37 (95% CI 0.21 to 0.64)] were less common in the PVB group, while more participants experienced urinary retention in the PVB group [RR 2.21 (95% CI 1.35 to 3.61)]. Similar levels of surgical and postoperative pulmonary complications were observed in each group. There was no difference between groups in critical care and hospital length of stay or in-hospital mortality. Forty-three participants (12%) in the PVB group and 33 participants (9%) in the TEB group experienced severe adverse events; only one in each group were considered related to allocated intervention.

Health-economic evaluation

The patients randomised to TEB group had slightly higher health resource costs than those in the PVB group. The mean (SD) total NHS cost per patient, 12 months after randomisation, was £16,216.94 (£8697.59) in the TEB group, and £16,137.27 (£10,154.76) in the PVB group. Thoracotomy costs contributed the most (around 52–53%) to the total NHS costs in both groups, followed by acute phase costs (around 41–42%). As no significant difference in the trial's primary outcome was identified between groups, the planned cost-effectiveness analysis in terms of cost per change in CPTP was not undertaken.

Utility values were slightly higher for the PVB group at baseline compared to the TEB group, but up to 12 months, the participants randomised to the TEB group reported slightly higher utility values than those randomised to the PVB group. However, the differences in the utility values were not statistically significant apart from at 12 months. Similarly, there were no statistically significant differences in QALY gains between the two groups, apart from between 6 and 12 months. At the 12-month time point, the overall QALY gain for the TEB group was higher than for the PVB group; however, this was not found to be statistically significant.

In the base-case analysis, the cost–utility analysis showed that costs and QALY gains for PVB and TEB were very similar, but that TEB was associated with slightly higher costs and QALYs when compared to PVB. The average cost for participant in the PVB arm was £16,137.27 compared with £16,216.94 for the TEB arm, and the QALY gain for the PVB arm was 0.73, compared with 0.77 for the TEB arm. The cost–utility analysis demonstrated that TEB resulted in slightly more QALYs at 12 months and was slightly less costly than PVB; however, the differences in costs and outcomes were not statistically significant at the 95% level.

The results of the sensitivity analysis showed considerable uncertainty was apparent in estimates of differences in costs and outcomes between the study arms. Including broader costs for the participants groups did not affect the study results, as such costs for both study groups were similar.

Discussion/interpretation

Principal findings and achievements

Paravertebral blockade is not superior to thoracic epidural blockade in preventing chronic post-thoracotomy pain

We demonstrate no evidence of a difference in the incidence of CPTP between patients receiving TEB versus PVB. Although CPTP defined according to our primary outcome definition of 'pain at its worst in the last week with regards to your chest' of ≥ 40 on a VAS occurred more commonly in patients receiving PVB (22% vs. 16%), this difference was not statistically significant. Across the study as whole, the 'signal' of no difference between techniques is compelling, being further supported by no differences in a large volume of secondary end-point data including CPTP defined by 'average' rather than 'worst' pain VAS, BPI and SF-MPQ-2 Inventory scores and the observation of similar analgesic use between groups over 12 months follow-up. While no consistent differences in outcomes were observed, our primary outcome result does strongly suggest that our original hypothesis of PVB being superior to TEB in preventing CPTP is unlikely to be true given the CI around the treatment effect estimate excluded a clinically meaningful difference in favour of PVB.

There are small differences in acute phase analgesia between techniques, but these are unlikely to be clinically significant

Multiple systematic reviews and meta-analyses have concluded that PVB and TEB provide equally effective analgesia in the acute postoperative phase.[14–18] Although we demonstrated a reduced 'worst pain' VAS on postoperative day 1 in the TEB group, the magnitude of this difference was slight, reflecting a mean difference (95% CI) of 7.7 mm (2.8 to 12.5). While this was matched by a

similar reduction in 'average pain' VAS on postoperative day 1, there was no difference between groups on days 2 and 3 nor on hospital discharge. Such a finding on postoperative day 1 is likely a reflection of our large sample size where we have been able to demonstrate a statistically significant, but at just 7.7 mm, one which falls short of the accepted 10 mm minimum clinically important difference[42] for a 100 mm VAS, further suggesting no clinically significant difference between groups.

The incidence of major and minor complications is not different between techniques

Among the clinical team caring for patients undergoing thoracotomy, the provision of excellent acute pain control is perceived to be of paramount importance not just in avoiding patient distress and minimising the risk of subsequent chronic pain development, but also in facilitating engagement with physiotherapy and early mobilisation following surgery and so reducing the risk of postoperative complications, particularly pulmonary complications. For this reason, as secondary end points, we built a robust postoperative complication data set into the TOPIC-2 trial defined according to the European Society of Thoracic Surgeons (ESTS) data set.[43] In keeping with previous reports, minor complications of pruritus[14] and hypotension[14–18] occurred more commonly in the TEB group. Urinary retention in the current study was however more common in patients receiving PVB, a finding at odds with previous reports, but which is likely confounded by the high rates of urinary catheter placement in the TEB group (33% in the PVB group vs. 72% in the TEB group). Overall, the incidence of both minor and major postoperative complications was no different between the two groups both for the ESTS-defined complications and for postoperative pulmonary complications defined according to the recent standardising end points in perioperative care core outcome set definitions.[44]

There are small by not statistically significant differences in cost-effectiveness between techniques

This trial-based economic evaluation analysed the cost-effectiveness of PVB compared with TEB in patients undergoing thoracotomy in a UK healthcare setting. The cost–utility analysis demonstrated that TEB produced an additional 0.04 QALYs when compared to PVB, and was associated with lower costs, but these differences were not statistically significant. The probabilistic sensitivity analysis demonstrated that there was considerable uncertainty around the estimates of differences in costs and outcomes between the study arms. The deterministic sensitivity analysis showed that the inclusion of productivity and private costs did not change the results of the evaluation.

Contribution to existing knowledge

We were motivated to carry out our trial by the combination of a Cochrane review highlighting a lack of robust RCT data concerning the effect of PVB versus TEB on CPTP[14] alongside a strong patient desire for research into strategies to reduce the incidence of chronic postsurgical pain.[45] The high-quality evidence provided by the TOPIC-2 trial has robustly addressed this evidence gap. Furthermore, with the literature to date reflected in a Cochrane Review of predominantly small studies, there remained other significant uncertainties around the relative effectiveness of these two analgesic techniques concerning acute phase analgesia and the impact of both techniques on postoperative complications which have also been addressed by the trial.

In light of the TOPIC-2 trial, we now have clear evidence for better informing our patients about acute and chronic postoperative pain that may be anticipated after surgery. This offers the NHS clinical team to develop an informed, personalised care plan considering patient preferences and balancing this with resource requirement.

Strengths and weakness

A significant strength of our study lies in its sample size; TOPIC-2 is, by some margin, the largest clinical trial comparing TEB and PVB conducted in the thoracic surgical population to date and recruited more patients than the 14 studies reported in the 2016 Cochrane Review recruited cumulatively.[14] By conducting the trial in 15 centres, in all 4 nations across the UK, we provide a widely generalisable result. Our trial was prospectively registered, and the protocol and statistical analysis plan were published prior to data analysis. Trial conduct was overseen by an independent Trial Steering Committee (TSC) throughout, and accumulating data were monitored for quality and safety by an independent Data Safety and Monitoring Committee. Protocol adherence appeared strong in both groups with low crossover rates. Episodes of non-adherence occurred in both groups primarily reflecting well-recognised technical challenges in the performance of both techniques. Adherence rates in the TOPIC-2 trial compare favourably with other large RCTs of perioperative epidural blockade.[46]

The TOPIC-2 trial was an open-label trial as we deemed it impractical to blind participants and unsafe to blind clinical care team completely to the study intervention. Lack of blinding could be considered a weakness of our study. We do not believe, however, that this lack of blinding will have introduced significant bias to our results as, firstly, primary outcome assessment took place 6 months after the original operative procedure and are therefore likely

to be resilient to the effects of imperfect concealment the intervention. Secondly, participants were not explicitly informed of their treatment allocation; in our preceding pilot feasibility study, most participants were not aware of their treatment allocation at follow-up, with slightly more participants in the PVB group unaware of the allocation compared to TEB.[10] Thirdly, we have no reason to suspect that patients would have preconceived ideas regarding the relative efficacy of either intervention.

Inevitably, by measuring our primary end point 6 months following the intervention (i.e. 6 months postoperatively), there was some loss to follow-up. Primary outcome results were available in 272 of 364 (74.7%) patients randomised to PVB and 269 of 373 (72.1%) patients randomised to TEB. Supported by our patient and public involvement (PPI) coinvestigators and the wider West Midlands Clinical Research Ambassador Group (CRAG) in devising strategies to maximise patient recruitment, we worked hard to maximise 6-month follow-up questionnaire return rates. Ultimately, loss to follow-up was in line with our projections at the time of sample size calculation where allowance was made for 10% patient mortality and a further 15% loss to follow-up. Follow-up rates were comparable between groups.

Across the study population as a whole, 19% of patients report moderate to severe CPTP 6 months postoperatively, a figure in keeping with previous reports,[3] but slightly less than we observed in our pilot feasibility study.[10] Although it is plausible this reduced event rate reflects a reducing prevalence of CPTP, potentially attributable to changes in surgical technique such as muscle- and nerve-sparing approaches, an incidence of 19% overall lies within the 95% CI of the incidence observed in our pilot population (30%; 95% CI: 18% to 42%). The fact that the observed rates were slightly lower than assumed in our sample size calculation may be inconsequential given the results so clearly did not support the hypothesis of superiority with PVB.

Take-home messages

1. Our trial sought to test the hypothesis that in adult patients undergoing open thoracotomy, the use of PVB for postoperative pain relief reduces the 6-month incidence of CPTP compared with TEB. We have conducted a large, robust, widely generalisable study and demonstrated that **the incidence of** CPTP **was comparable between two groups**. Our results allow us to reasonably confidently reject the hypothesis. Our study also supports previous data in demonstrating that in the acute phase both techniques provide comparable analgesia. Overall, the incidence of both minor and major postoperative complications was not different between the two techniques, although TEB was associated with an increased incidence of hypotension and pruritus.
2. Our PPI coinvestigators emphasise that we would be doing our patients a disservice by not highlighting the 'take-home message' that though we were not able to demonstrate that PVB is any more effective in preventing CPTP than TEB, there remains a **striking burden of chronic postsurgical pain following thoracic surgery. Across the study population, 19% of patients report moderate to severe** CPTP **6 months postoperatively.**
3. This is the first health-economic analysis of PVB compared with TEB in thoracotomy patients the UK, adopting both a healthcare and societal perspective. The analysis demonstrated that TEB **produced an additional 0.04 QALYs when compared to** PVB**, and was associated with higher costs, but these differences were not statistically significant.**

Reflections on the project and what could have been done differently

Patient endorsement of the study question

As discussed elsewhere (see *Engagement with partners and stakeholders*), PPI involvement was strong within TOPIC-2. Further, embarking on the trial was motivated by the James Lind Alliance Anaesthesia and Perioperative Care Priority Setting Partnership, involving professional and patients/carer stakeholder organisations identifying the question of 'what can we do to stop patients developing chronic pain after surgery?' as a top 10 research priority.[45] A striking finding of the QRI (discussed in *Qualitative recruitment initiative*) embedded into the first year of the trial was that recruitment rates were exceedingly high when patients were approached to take part in the study (such that there was little potential of improving recruitment by increasing the eligibility to randomisation rate). Patients believed in the study question, and when offered the opportunity they were keen to take part in the study, but study delivery was hampered by downgrade with clinician equipoise (discussed in *Challenges faced and limitations*). On reflection, though we took great efforts to ensure the patient voice was heard throughout study conduct, it is plausible that further engagement work highlighting to clinicians the high levels of patient endorsement of the study question could have improved clinicians' buy-in.

Strategies that could have been employed to boost recruitment

For reasons discussed more completely below (see *Challenges faced and limitations*), recruitment to the TOPIC-2 trial was always slower than anticipated. In light of this, we reflect that perhaps more significant changes to trial design and delivery could have been implemented at an earlier stage. These include:

1. **Involvement of overseas centres:** Colleagues in European and Australasian centres expressed great interest in joining the TOPIC-2 trial and anecdotally appeared to have greater equipoise surrounding the study question. Opening the trial to overseas centres was proposed by both TMG and TSC in response to low recruitment rates, but this was not aligned with the National Institute for Health and Care Research (NIHR) funding focusing on investigating the NHS clinical and cost-effectiveness.
2. **Expansion to other surgical groups undergoing thoracotomy:** Eighty-five per cent of patients recruited to the TOPIC-2 trial underwent thoracotomy for resection of lung cancer. However, as a means to surgically access structures within the chest, thoracotomy is not the sole preserve of the thoracic surgeon and is also performed during some oesophagectomy and vascular surgeries. To avoid heterogeneity in the patient sample (many oesophagectomy patients, e.g. undergo simultaneous thoracotomy and laparotomy increasing both the risks of surgery and chronic pain development), it was elected not to pursue recruitment in other surgical groups.

Challenges faced and limitations

Throughout the trial, recruitment rates fell below target due to **three main challenges**:

Falling open thoracotomy rates

Surgery across all specialties is undergoing a paradigm shift from traditional 'open' surgeries to the increasing use of 'minimally invasive' surgical techniques. At the time of trial conception, this was reflected in UK thoracic surgery by increasing numbers of 'VATS', but a stable rate of thoracotomies. Since then, though not reflected in national data which lag behind contemporary practice,[47] sites report a reduction in thoracotomy rates and therefore a reduction in the number of patients eligible for trial recruitment. A reduction in thoracotomy rates has been further accelerated by the adoption in many centres of 'robotically assisted thoracic surgery' which was not foreseen but has facilitated minimally invasive surgery in some settings where VATS was unable to provide a minimally invasive alternative.

Equipoise

Despite exhaustive efforts and in-principal agreements to participate at the time of funding submission, we were unable to engage any more than 15 (of a planned 20) participating sites. Difficulty engaging sites largely reflected the challenge of equipoise around the study question among the clinical community with potential study sites declining to take part because they perceived one or other of the study techniques to be more effective (sites declined to participate citing a lack of equipoise in favour of both TEB and PVB). This reinforces the importance of the study question reflecting high levels of uncertainty but strongly held beliefs (in the absence of evidence) among clinicians.

COVID-19

As with many clinical trials, recruitment to TOPIC-2 struggled significantly due to the COVID-19 pandemic. As with all other non-Urgent Public Health research, the trial was formally suspended between March and July 2020. Following an online 'relaunch' event, recruitment recommenced but failed to reach pre-pandemic levels and was further impacted by subsequent pandemic waves. Throughout the remainder of 2020 and much of 2021, sites reported reduced capacity to recruit to TOPIC-2 reflecting: redeployment of research delivery staff to front-line duties; redeployment of research delivery staff to work on Urgent Public Health studies; elevated rates of staff sickness absence; elevated proportion of staff 'catching-up' on much-needed annual leave not taken during the pandemic; relocation of surgical services during and post pandemic to areas (e.g. private facilities) where research delivery infrastructure was not available. Due to the well-documented increased pressures on research delivery infrastructure post pandemic, a number of study sites never resumed recruitment post pandemic.

As a combination of these challenges, it became apparent that achieving our target sample size was not feasible. For this reason, in consultation with the funder, and with the support of the TSC and Independent Data Safety Monitoring Committee, but blind to the accumulated study data, we elected to reduce the target sample size (from 1026 to 770) reflecting a reduction in statistical power from 90% to 80%.

Engagement with partners and stakeholders

Throughout its design and conduct, the TOPIC-2 trial has engaged widely with relevant partners and stakeholders.

Patient and public involvement

The critical involvement of patient coinvestigators is described below (see *Patient and public involvement*). In addition to coinvestigators' involvement, in the design phase we engaged with the West Midlands CRAG, the Society of Cardiothoracic Surgeons Thoracic Surgery (SCTS) Research Collaborative Patient and Public Involvement group (RESOLVE – RESOLVE PPI | SCTS) and the National Institute of Academic Anaesthesia (NIAA)/ Health Science research centre's Patient, Carer, Public Involvement and Engagement group (PCPIE, www.niaa-hsrc.org.uk/), all of whom were very supportive of the trial objectives and provided insight into the trial and patient-facing material design. Our patient coinvestigators benefited from being able to consult with CRAG for advice on several occasions during the trial (such as when trying to brainstorm retention strategies to improve follow-up questionnaire return rates). The PPI investigators will submit the manuscript of *The PPIE in the journey of the TOPIC trials* to a journal.

Perioperative Medicine Clinical Trials Network

Established in 2016, the UK Perioperative Medicine Clinical Trials Network (POMCTN www.pomctn.org.uk) has been running since 2016 with objectives to develop and support large-scale world-class clinical trials in Anaesthesia, Perioperative and Pain Medicine. TOPIC-2 was adopted as a CTN supported trial; BS was awarded a CTN trial training fellow by involving the TOPIC-2 trial delivery. Through its distribution list and biannual meetings, POMCTN provided a route to access the wider UK perioperative research community aiding site engagement activity.

We have also been working with POMCTN/NIAA in trial dissemination activities. The TOPIC-2 results were presented publicly for the first time at a 'breaking trials' session within the NIAA's flagship 'Anaesthesia Research 2024' conference on 29 November 2024.

Association of Cardiothoracic Anaesthetists

Promoted through their 'research subcommittee', the Association of Cardiothoracic Anaesthesia and Critical Care (ACTACC) provided an opportunity to engage with UK clinical thoracic anaesthetic workforce. TOPIC-2 was presented at several ACTACC scientific congress' greatly aiding conversations with sites.

We have also been working with ACTACC in trial dissemination activities. It is planned to present the TOPIC-2 trial results at the ACTACC annual scientific meeting in Leicester in June 2025 ensuring maximum exposure of the trial's findings to the clinical thoracic anaesthetic workforce.

Society of Cardiothoracic Surgeons

The TOPIC-2 trial was presented regularly at the SCTS annual scientific meetings allowing engagement with the UK thoracic surgical community. In the development phase, the concept and proposed design were presented to the national thoracic surgery PPI group 'RESOLVE'.

We have also been working with SCTS in trial dissemination activities. The TOPIC-2 trial results were presented at the SCTS annual scientific meeting in Edinburgh in March 2025 ensuring maximum exposure of the trial's findings to the clinical thoracic surgical workforce.

Statistician and health-economist career development

The TOPIC-2 methodologists have played a vital role in the design and successful completion of the study. The trial has brought opportunities for two early career researchers (statistician and health economist) to grow in their career trajectories through their contributions to the delivery of an important clinical trial. The trial follows the NIHR inclusive principles by recognising the equality of their input. Future work using the TOPIC-2 data is planned and may include methodological contributions to several studies, including individual patient data meta-analysis and prognostic studies (e.g. predictors of chronic pain).

Trial intervention training

Within the NHS, TEB and PVB are widely practised routine techniques within certified competence skill set of most thoracic anaesthetists. However, for TOPIC-2 trial intervention, two online training videos detailing insertion of thoracic epidural and paravertebral blocks were produced alongside supplementary written step-by-step guides. All anaesthetists participating in the trial were mandated to review either the videos and/or written material and confirm their ability to perform the techniques. Further training, if required, was provided by trial-designated trainers who travelled to participating sites to both demonstrate and observe performance if requested.

TOPIC trial patient and public involvement short form

The following account of PPI in TOPIC-2 is based on the Guidance for Reporting Involvement of Patients and the Public short form reporting checklist of PPI in research.

Aim

In TOPIC-2, we sought to develop a strategy to enable patients and members of the public to make a meaningful contribution to the design, delivery and dissemination of the trial.

Methods

Patient and public involvement has been integral to this trial from the outset. Patients with a lived understanding of chronic pain following thoracic surgery were consulted, and their views were essential to the design of our NIHR Research for Patient Benefit-funded TOPIC-1 study, which underpinned feasibility data for TOPIC-2.

Those consulted established that quality of life and pain management were central concerns for this cohort of patients. This was further confirmed when '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.[45]

Our approach to engage with patients and members of the public consisted primarily of the following strategies:

- Two patient and public representatives [Andrew Worrall (AW) and Stephen Grant (SG)] joined the TMG and were coapplicants. SG has lived experience of chronic pain following thoracic surgery and was integral to the success of the feasibility trial (TOPIC-1). AW has extensive experience of PPI, having been a member and chair of a Comprehensive Local Research Network and a member of the West Midlands Research for Patient Benefit board. AW has attended more than 90% of TMG meetings. PPI representation has been stable and involved throughout.
- A patient and public representative also sat as an independent member of the TSC.
- We worked with the CRAG at the University Hospitals Birmingham NHS Foundation Trust (UHB) to recruit a diverse group (gender, ethnicity, personal experience of critical illness/surgery and research experience) of PPI representatives. Representatives focused on providing plain English explanations of the trial and ensuring the burden of the trial was not unduly excessive for patients. Once the trial was active. PPIs focused on devising strategies for improving recruitment and retention and raising awareness of patient concerns. They were listened to and included in decision-making by the trialists. Advisory group activity heightened following COVID-19 as restarting trial activity was discussed. The chair of CRAG (AW) is a coapplicant and presented trial updates to the wider group on a quarterly basis. The group met monthly throughout the duration of the trial and had a mean attendance of six individuals.

Discussions and conclusions

The PPI representatives are helping to develop a detailed dissemination plan for the trial. Public contributors will design a 'plain English' summary of the study findings suitable for dissemination to a non-clinical audience. The trial summary will be posted to participants who have requested a copy during the initial trial consent. PPI representatives will design presentation materials for dissemination to key stakeholder groups and will collaborate with consumer organisations such as Cancer Research UK, the British Lung Foundation and the British Pain Society to bring the results of this study to a larger lay audience. PPI have drawn attention to the significant group of patients who continue to experience long-term postoperative pain and will advocate for further research in this area.

Reflection

Though not as diverse as we would have wished, PPI was successfully embedded throughout the trial, despite the challenges of COVID-19. AW coauthored the protocol publication. Both AW and SG are coauthors on this publication with an acknowledgement to CRAG. AW has been integral to writing NIHR reports, the lay summary and supplementary sections for this publication.

National Institute for Health and Care Research equality, diversity and inclusion strategy

TOPIC-2 had excellent gender balance, with 44% of participants identifying as female and 56% identifying as male. Given the vast majority (85%) of operations were due to lung cancer, we can be confident that we managed to attain a very similar gender distribution in the trial to that seen in the UK lung cancer population at a national level.[48]

Lung cancer is known to impact those from an Asian, Black and Chinese background disproportionally.[49] Our 15 recruiting centres accommodated all 4 UK nations, including centres in diverse ethnic regions such as 2 sites in Birmingham, 1 in Coventry and 1 in Leicester. We had a very high conversion rate from those eligible to those randomised (64%). Given our relatively broad eligibility criteria, we can be reasonably confident that our population mirrored the national rate of ethnic groupings. Unfortunately, we did not have the foresight to collect

ethnicity data, so we are unable to confirm this was the case. This is a limitation of the study. In a similar vein, our study design predates current recommendations on research inclusion.[50] If it were designed in the current day, we would have placed extra emphasis on making sure our recruitment strategy included enhanced ability to recruit those speaking a non-native language.

In terms of the research team, this included 19 members, of which 6 (32%) were from an ethnic minority and 9 (47%) were women. Of the eight independent members of the Trial Oversight Committees (TSC and Data Monitoring Committee), four (50%) were women and none from an ethnic minority.

Learning, dissemination and impact

Learning

As discussed in *Challenges faced and limitations*, the challenge of strongly held clinical belief compromising clinician equipoise is a significant learning point. The obvious potential to cause patient harm through performance of a regional anaesthetic technique makes this a particularly emotive topic for clinicians. In any future trial, greater provision of time and funding for patient advocacy input would be advantageous.

Dissemination activities

The TOPIC-2 trial data have only just become available, with manuscript submission for peer-reviewed publication taking place contemporaneously with synopsis writing. It is too early therefore to evaluate the impact of the trial results.

In order to ensure we provide maximum impact from the trial, we have a number of dissemination activities planned:

- The trial has been presented in a 'breaking trials session' at the UK NIAA 'Anaesthesia Research 2024' conference on 29 November 2024.
- In addition to presentation to the research community however, it is essential that we bring the TOPIC-2 trial results to the clinical thoracic surgical and anaesthetic workforce. To this end, it is planned to present the trial results at the Association of Anaesthetists' Thoracic Anaesthesia Update in March 2025, the ACTACC annual scientific meeting in Leicester in June 2025 and the Society of Cardiothoracic Surgeons annual scientific meeting in Edinburgh in March 2025. These flagship meetings are the core providers of continuing education in thoracic anaesthesia and surgery in the UK.
- To maximise international impact, we have submitted the TOPIC-2 trial for consideration for presentation in a 'late breaking trials session' to the US Society of Cardiovascular Anaesthesiologists Annual Meeting in April 2025.
- We are working with our patient coinvestigators to produce a 'plain English' summary of the study findings which we will post to study participants and cascade to the CRAG, PCPIE and RESOLVES PPI groups with which we have engaged. In addition, it is anticipated the trial will be presented to the RESOLVES group at an upcoming meeting.

Impact

To understand the potential impact of the TOPIC-2 trial result, it is important to understand the nuances of the clinical context. Over the last 20 years, provision of analgesia for patients undergoing thoracotomy has evolved from almost ubiquitous use of the historical gold-standard TEB technique to increased uptake of PVB[11–13]. This has been propagated by a number of factors:

- Increasing familiarity with PVB and reducing experience in TEB due to increased rates of minimally invasive thoracic (MIT) surgery (PVB is commonly used to provide analgesia for MIT surgery, but TEB is not).
- Concerns among physicians regarding the rare but very significant complications of TEB such as epidural haematoma, infection, nerve damage or paralysis.
- Resource limitation and changes in patient pathways such that TEB is more difficult (or impossible) to deliver. Patients receiving TEB are traditionally cared for in a critical care/high-dependency unit setting while patients receiving PVB are deemed safe to care for on the ward. As critical care resource is increasingly stretched, pathways which avoid, what by some is perceived as 'unnecessary critical care admission', are increasingly sought.
- Systematic review data suggesting equivalent performance of TEB and PVB[14] (i.e. if familiarity is less, risks are greater, and appropriate resource is limited why not favour PVB if both blocks are equivalent?).

The TOPIC-2 trial sought to address two key evidence gaps in this area:

1. effectiveness of these techniques in reducing the incidence of CPTP
2. health-economic analysis of TEB verses PVB.

The clinical findings of the TOPIC-2 trial suggest equivalent effectiveness of PVB and TEB, both in terms of chronic pain

prevention (the trial's primary objective) and in supporting previous systematic review findings of equivalent acute phase analgesia and no difference in complication rates. Examined solely in the clinical context, these findings are likely to continue to support the observed evolution in practice away from TEB. Similarly, the economic analysis demonstrated that costs and outcomes were similar across the trial arms, challenging clinician concerns around the resource impact of TEB. While TEB produced an additional QALYs when compared to PVB, and was associated with higher costs, these differences were not statistically significant.

Implications for decision-makers

Thoracic epidural blockade and PVB appear to have equivalent clinical and cost-effectiveness. The economic analysis demonstrated that costs and outcomes were similar across study groups. Although TEB produced additional QALYs when compared to PVB, and was associated with higher costs, these differences were not statistically significant. The sensitivity analysis demonstrated considerable uncertainty around the trial estimates.

As such, we believe both techniques should remain useful tools in the thoracic anaesthetist and surgeon's armamentarium, allowing appropriate deployment when the clinical situation demands, and facilitating individualised analgesic plans to be made for each patient.

Research recommendations

Strategies to reduce chronic pain following surgery

Our PPI coinvestigators mandate we emphasise this point. Though PVB did not reduce the rate of CPTP compared to TEB, there remains a striking burden of CPTP. Although not examined directly in this analysis, as a clinical community we must remain cognisant of the well-recognised, profound and widespread effects of CPTP on patient function and quality of life and continue to seek interventions to ameliorate this disabling condition.

Analgesic strategies for patients undergoing minimally invasive thoracic surgery

As thoracic surgery is increasingly delivered via a minimally invasive surgical approach, research needs to focus on the safe, effective and patient-centred delivery of care around the time of minimally invasive surgery. Chronic pain remains a significant issue following minimally invasive surgery, yet there is even greater uncertainty regarding optimal analgesic techniques in this setting. A wide range of regional local anaesthetic techniques are being employed without evidence regarding the comparative effectiveness nor crucial aspects of care delivery such as the need for catheter placement or the timing of block performance.

Strategies to tackle clinician (lack of) clinician equipoise

As discussed above, the TOPIC-2 trial struggled to engage centres in the face of a lack of clinician equipoise despite strong patient endorsement of the study question and a lack of definitive evidence in favour of either trial intervention. Clinicians expressed strongly held beliefs if favour of both interventions. This is a challenging area, but there is no doubt that more work is required to provide increased understanding of clinician decision-making processes and to further promote research culture in the clinical environment.

Conclusions

We provide high-quality data from a robust, multicentre RCT addressing a key evidence gap in the perioperative care of patients undergoing open chest surgery. In our study, PVB and TEB appear to be equivalent in clinical and cost-effectiveness in preventing chronic post-thoracotomy at 6 months; this may be paving the way for both techniques likely to continue in NHS thoracic settings, based on clinician and patient's choices. To address the further knowledge gap in this area, we will use the full TOPIC-2 data sets, defined according to the ESTS data set, to explore the trajectory of the development from acute to chronic post-surgery pain.

Additional information

CRediT contribution statement

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Members of the Trial Management Group:

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Other Current and Former Birmingham Clinical Trials Unit Staff:

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TOPIC-2 Recruiting sites:

Participants: The authors also gratefully acknowledge the support of the participants who consented and were randomised into

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TOPIC-2, as well as those who were approached and considered participation in TOPIC-2.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

Ethics approval for the trial was obtained from the South-East Scotland Research Ethics Committee (REC 18/SS/0131) on 8 November 2018. All participants gave written informed consent before participation. The trial was being conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Data Protection Act 1998) and the Principles of GCP.

Information governance statement

All personal information was processed in accordance with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, the University of Birmingham and NHS West Midlands is the Data Controller. The University of Birmingham Data Protection Officer here: legalservices@contacts.bham.ac.uk

The University of Birmingham is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, the University of Birmingham is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: www.birmingham.ac.uk/university/leadership/governance/policies-regs/data-protection

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

This trial is registered as NCT03677856.

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Award publications

This synopsis provided an overview of the research award *TOPIC 2: A Randomised Controlled Trial to investigate the effectiveness of ThOracic Epidural and Paravertebral Blockade In reducing Chronic Post- Thoracotomy Pain: 2*.

Other articles are planned to be published as part of this thread. These were still under review when this synopsis was published. The following preprint versions are available for the reader; please be aware these may not have been peer reviewed:

Shelley B, Middleton L, Boyles R, Gilbert M, Goebel A, Goldsmith I, *et al.* Thoracic epidural versus paravertebral blockade for reducing chronic post-thoracotomy pain (TOPIC-2): an open-label, multicentre, randomised controlled trial. *medRxiv* 2025. https://doi.org/10.1101/2025.08.07.25333201

Javed M, Jackson L, Middleton L, Shelley B, Summers H, Boyles R, *et al.* The cost-effectiveness of thoracic epidural versus paravertebral blockade in reducing chronic post-thoracotomy pain – a trial-based economic evaluation. *medRxiv* 2025. https://doi.org/10.1101/2025.08.07.25333206

For more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/16/111/111).

Additional outputs

Study protocol:

Shelley B, Goebel A, Grant S, Jackson L, Jarrett H, Jepson M, *et al*. Study protocol for a randomised controlled trial to investigate the effectiveness of thoracic epidural and paravertebral blockade in reducing chronic post-thoracotomy pain: 2 (TOPIC 2). *Trials* 2023;**24**:748. https://doi.org/10.1186/s13063-023-07463-1

About this synopsis

The contractual start date for this research was in May 2018. This article began editorial review in January 2025 and was accepted for publication in July 2025. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Health Technology Assessment editors and publisher have tried to ensure the accuracy of the authors' article and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this synopsis.

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List of abbreviations

ACTACC	Association of Cardiothoracic Anaesthesia and Critical Care
BPI	Brief Pain Inventory
COVID-19	coronavirus disease 2019
CPTP	chronic post-thoracotomy pain
CRAG	Clinical Research Ambassador Group
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
ESTS	European Society of Thoracic Surgeons
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
ITT	intention to treat
MIT	minimally invasive thoracic
NIAA	National Institute of Academic Anaesthesia
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PCPIE	Patient, Carer, Public Involvement and Engagement
POMCTN	Perioperative Medicine Clinical Trials Network
PPI	patient and public involvement
PVB	paravertebral blockade
QALY	quality-adjusted life-year
QRI	qualitative recruitment initiative
QuinteT	Qualitative Research Integrated into Trials
RCT	randomised controlled trial
SCTS	Society of Cardiothoracic Surgeons Thoracic Surgery
SF-MPQ-2	Short Form McGill Pain Questionnaire 2
TEB	thoracic epidural blockade
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	visual analogue scale
VATS	video-assisted thoracoscopic surgery

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