Statistical analysis plan for the OPtriAL: a three-arm multicentre pragmatic randomised controlled trial for optimal postoperative pain management after thoracoscopic lung resection

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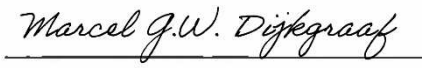

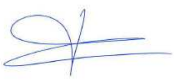

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Abstract

Background:

Adequate pain control after thoracoscopic surgery for lung resections is important to improve postoperative mobilization and recovery, to prevent pulmonary complications. Despite increased use of thoracoscopic surgery, clinically relevant pain is still present in 38% of the patients. Although frequently performed, guidelines report no consensus on the preferred analgesic technique during thoracoscopic surgery. Thoracic epidural analgesia is currently the standard of care due to its clear analgesic effect, however, related adverse events have triggered a growing interest in alternative locoregional analgesic techniques, such as paravertebral block or intercostal nerve block. Until now, evidence to change the standard of care is scarce. The OPtriAL evaluates whether a continuous paravertebral block or a single-shot intercostal nerve block are non-inferior to thoracic epidural analgesia regarding pain and superior regarding quality of recovery.

Methods:

We established a statistical analysis plan for transparent reporting of data analysis regarding the OPtriAL study. For this study, patients undergoing thoracoscopic anatomical lung resection are randomized into one of three arms: thoracic epidural analgesia, continuous paravertebral block or single-shot intercostal nerve block. Co-primary outcomes are: a) proportion of pain scores ≥ 4 as assessed with the numerical rating scale during postoperative day 0 until postoperative day 2 and b) quality of recovery, measured with the quality of recovery-15 questionnaire on postoperative days 1 and 2. In order to be non-inferior, the upper margin of the 98.65% one-sided confidence interval of the difference in mean proportions of pain scores ≥ 4 between the continuous paravertebral block and single-shot intercostal nerve block, both separately compared with the thoracic epidural analgesia, may not exceed 17.5% (predefined non-inferiority margin). Intention-to-treat and per-protocol analyses should both indicate non-inferiority to implement the intervention techniques as relevant alternatives to thoracic epidural analgesia. We expect a counterbalancing gain in quality of

recovery, which will be tested for superiority. Secondary outcomes such as length of stay, complications and patient mobility will also be tested for superiority.

Discussion:

The results of the OPtriAL will provide level 1b evidence to optimize postoperative pain management and perioperative care for thoracoscopic anatomical lung resections.

Trial registration: The trial is registered at the Netherlands Trial Register (NTR) on February 1st, 2021 (NL9243). The NTR is no longer available since June 24th, 2022 and therefore a revised protocol (Version 3, date May 6th, 2022) has been registered at ClinicalTrials.gov on August 5th, 2022 (NCT05491239).

SAP version: Version 1, dd 11-10-2023

Protocol: This statistical analysis plan has been written based on the information contained in the published study protocol version 3 (1).

Keywords: Statistics, Clinical trial, Pain, VATS, Lung surgery

Background and rationale

Considerable improvements have been made by the implementation of thoracoscopic surgery for anatomical lung resections compared to open surgery in terms of less postoperative pain, shorter length of stay (LOS) and faster recovery (2), however, acute postoperative pain is still present in a large proportion of patients (3). Adequate pain control is important to improve postoperative mobilization, recovery and patient satisfaction, and prevent pulmonary complications. Whereas guidelines lack consensus on the preferred analgesic technique, thoracic epidural analgesia (TEA) is considered the standard of care due to its clear analgesic effect. However, associated adverse events have triggered a growing interest in alternative loco-regional analgesic techniques. Recent PROSPECT (4) and European guidelines (5) recommend the use of loco-regional analgesic techniques, including paravertebral block (PVB), intercostal nerve block (ICNB) and erector spinae block. Until now, evidence to change the standard of care is scarce and a recent systematic review reports great inter-study heterogeneity (6) and the need of more rigorous clinical evidence from a randomized clinical trial. The OPtriAL is a three-arm multicentre pragmatic randomized trial comparing continuous PVB, single-shot ICNB and TEA regarding pain and quality of recovery (QoR) in patients undergoing thoracoscopic anatomical lung resection. The objective of the OPtriAL is to provide high quality level 1b evidence to be implemented in enhanced recovery after thoracic surgery (ERATS) protocols. We hypothesize that continuous PVB or single-shot ICNB is non-inferior to TEA regarding postoperative pain but superior regarding QoR. This may imply faster postoperative mobilization, reduced morbidity, and shorter hospitalization. Loco-regional techniques may therefore reduce health care costs and improve patient satisfaction.

Summary of the study protocol

The OPtriAL (Optimal postoperative Pain management After thoracoscopic Lung resection) is a three-arm multicentre pragmatic randomized controlled trial comparing TEA, continuous PVB and single-

shot ICNB in adult patients undergoing thoracoscopic anatomical lung resection. The study comprises two co-primary outcomes with different designs: a non-inferiority design for the outcome 'pain' and a concomitant superiority design for the outcome 'quality of recovery'.

Adult patients (>18 years) referred for thoracoscopic anatomic lung resection (segmentectomy, (bi)lobectomy and pneumonectomy for either benign or malignant disease) are eligible for the trial. We exclude patients with a contraindication for one of the analgesic techniques, chronic use of opioids, a high probability of conversion to thoracotomy or in case of insufficient Dutch proficiency. Written informed consent is obtained from each participating patient before randomisation. Patients are randomized in a 1:1:1 ratio for one of the three analgesic techniques by a computerized database (Research Manager) with an unchangeable computer-generated number. Randomization is done in random block sizes of 6, 9 and 12. As anaesthesia and surgical protocols may slightly differ between hospitals, randomization is stratified by treatment centre. Blinding is unfeasible due to clear visible differences of the analgesic techniques and would potentially compromise the safety of the patient (analgesic catheter, indwelling urinary catheter, mobility with or without prerequisites).

The first co-primary outcome relates to pain and the second to QoR. Pain is measured with the numerical rating scale (NRS 0-10; 0=no pain, 10=worst imaginable pain). A NRS score <4 indicates acceptable pain and ≥4 indicates unacceptable pain as it implies the clinical need for additional analgesia. Therefore, our primary outcome 'pain' for non-inferiority is expressed as the proportion of postoperative NRS scores in rest ≥4, defined as the number of NRS ≥4 measurements divided by the total number of NRS measurements obtained from postoperative day (POD) 0 until POD 2. Each patient has a maximum of 8 measurements: at the recovery room, the evening of the day of the operation, and in the morning, afternoon and evening of POD 1 and 2. Superiority of the second co-primary outcome 'QoR' is measured with the QoR-15 questionnaire (lowest score of 0 and highest score of 150) at POD 1 and POD 2.

Non-inferiority for pain is obtained only if the upper limit of the 98.65% one-sided confidence interval (CI) of the differences of mean proportion of NRS ≥4 between the PVB versus TEA and ICNB versus TEA remains below the predetermined absolute margin of 17.5% in the intention-to-treat (ITT) analysis as well as in the per-protocol (PP) analysis. This non-inferiority margin is based on data from a previous pilot study, in which the proportion of pain scores ≥ 4 in a group of patients receiving TEA was 17.57% (SD 19.57) and in patients receiving continuous locoregional analgesia 21.21% (SD 23.33). Since the baseline of 17.57% of moments of pain in the control group is low, we accept an absolute margin of 17.5% from a clinical point of view. This margin of non-inferiority, accepting more moments of pain in the intervention techniques as compared to the control group, is justifiable in combination with superiority regarding QoR. Superiority regarding QoR is defined as a significantly higher mean score during POD 1 and POD 2 ($p < 0.027$) in the ITT analysis. Taking the mean QoR score during POD 1 and POD 2 is a simplifying improvement of the original superiority definition in the published study protocol (1) without affecting the sample size calculation.

Secondary outcomes are: 1) pain scores during rest and mobilization at the recovery room, in the evening of the day of operation, and in the morning, afternoon and evening on POD 1 until POD 3, and at 2-3 weeks follow-up; 2) proportion of NRS scores ≥4 during mobilization during POD 0 until 2; 3) QoR-15 at POD 0, POD 3 and 2-3 weeks follow-up; 4) cumulative use of opioids and analgesics at POD 0 until 3 and the plain use of opioids at 2-3 weeks follow-up; 5) postoperative complications until POD 30; 6) hospitalisation; 7) patient satisfaction at POD 0 until 3; 8) time to removal of the chest tube; 9) time of an indwelling urinary catheter; 10) degree of mobility at POD 0 until 3 and 11) cost-effectiveness analysis (separate analysis).

The sample size calculation resulted in 450 patients in total (150 for each randomization group) to demonstrate non-inferiority regarding proportion of NRS measurements ≥4 (power 99%, one-sided Type 1 error of 0.0135) as well as superiority regarding QoR (power 90%, two-sided Type 1-error of 0.027), taking into account an assumed 12.6% drop-out for conversions to thoracotomy (in the Netherlands, data from the Dutch Lung Cancer Audit from 2017) and controlling for the family-wise

error rate associated with the comparison of the two experimental groups (PVB and ICNB) with the same control group TEA (1).

Interim and final analysis

Since the point estimators regarding proportion of measurements with a NRS ≥4, used in our sample size calculation for non-inferiority, were based on a small pilot study they may have limited reliability. We therefore established a Data Safety Monitoring Board (DSMB), including a methodologist, statistician and two clinical experts (anaesthesiologist and thoracic surgeon) to assess whether our study generates sufficient power to answer the research question. When 50% of the observations in the TEA group (control) were completed (n=75), the DSMB performed an interim analysis to evaluate the point estimator and variance of the proportion of NRS measurements ≥4 of the control group and advised whether adjustment of our sample size was necessary. The DSMB only had access to all patients who underwent TEA and could warn the research team of potential risk factors and suspension of inclusions. The interim analysis by the DSMB was performed in January 2023. Based on pain scores of 70 complete TEA patients (4 patients had missing data and 1 patient was treated as TEA but randomized for ICNB) in the ITT analysis, no changes in the sample size were required. The final analysis will be performed when all data of 450 patients is collected. No specific stopping rules apply since the OPtriAL has been classified as having negligible risk for study subjects. The SPIRIT flow diagram in Table 1 of the published protocol (1) demonstrates a complete overview of the schedule of assessments.

Statistical principles

The statistical analysis plan is formulated using the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials and the completed checklist can be found in Appendix B. All tables and figures shown are presented with hypothetical values to help visualize the end result.

Analysis principles and general considerations

Continuous data will be reported as means with standard deviation (SD) or confidence intervals (CI), or medians with interquartile range (IQR) and will be compared between groups using the unpaired t-test or Mann-Whitney U, depending on the distribution of the data. Equality of variances for TEA and PVB, respectively ICNB, will be assessed with Levene's test. Categorical data will be presented as counts and percentages and data will be compared using Mantel-Haenszel Chi-squared test. In case of zero cell counts and when pooling of categories is not opportune, the Fisher's exact test will be used (7,8). For all secondary outcome measures, the CI and/or p-values will be provided to express the level of statistical significance per outcome without additional correction for multiplicity (also $p<0.027$). An overview of the planned statistical tests per outcome measure for group comparisons can be found in the Supplemental material (Appendix A).

Protocol violation, adherence and deviation

Protocol violation is defined as non-adherence to the eligibility criteria, randomization process and study procedures, dictating that all patients should participate voluntarily and undergo an anatomical lung resection by VATS and one of the analgesic techniques (TEA, PVB or ICNB).

Protocol adherence defines that control patients should proceed to PVB catheter placement in case TEA catheter placement was unsuccessful; in case PVB too was unsuccessful, then ICNB should be done. Participants receiving TEA or PVB should have a provisional stop of the continuous analgesia at POD 2 and patients receiving TEA should have opioids administered through the epidural continuous

mixture. Accidental luxation of the TEA or PVB catheter after surgery will not be seen as non-adherence.

Although the use of ERATS guidelines for enhanced postoperative recovery were advised by the protocol, it is expected that the level of implementation of each aspect of ERATS differs per hospital, for example the strict use of dexamethasone and 5-HT_3 receptor antagonists. In addition, the availability of specific local anaesthetics (e.g. bupivacaine or ropivacaine) may vary and induce small between-hospital differences. To ensure equal distribution of small differences in ERATS aspects, we used treatment centre as stratification factor. Incomplete primary or secondary endpoints are considered a protocol deviation and are handled as missing data.

Intention-to-treat and per-protocol populations

Protocol violations such as not meeting the eligibility criteria, withdrawal from the randomization process, not performing an anatomical lung resection by VATS (conversion to thoracotomy, wedge resection or no resection), not utilizing TEA, PVB or ICNB as analgesic technique, or death on the day of the operation (resulting in unobtainable study results), will result in exclusion of the primary analysis. The ITT population will include all remaining randomized patients.

The PP population will include all patients from the ITT population who have adhered to the protocol. Patients will not be included in the PP population when the order of locoregional analgesic techniques in case of unsuccessful performance (TEA, PVB and then ICNB), the provisional stop at POD 2 in case of TEA of PVB, or when the addition of opioids to the epidural mixture were violated.

Trial population

All screened patients assessed for eligibility and receiving the patient information folder will be recorded. The number of patients not randomized or excluded from the ITT and PP analysis will be

reported with reasons (e.g. withdrawal or lost to follow-up). Similarly, the number of randomized patients per analgesic group as well as the number of patients in the ITT and PP analysis will be reported. Progress of all participants through the trial is depicted in Figure 1.

Baseline characteristics

Baseline characteristics will be described by trial arm as illustrated in Table 1 and assessed descriptively for the ITT group. In case of missing data, the denominator will not match with the total number of patients and this will be indicated in the corresponding table. Missing baseline characteristics will not be imputed.

Since stratification and randomization are applied to ensure a balanced distribution of baseline characteristics, we assume any differences to be caused by chance and to be a property of the sample, not of the population. Nevertheless, an imbalance of prognostic factors should not be ignored as it can influence the estimation of treatment effects. Therefore, all baseline characteristics in Table 1 will be compared between TEA versus PVB and TEA versus ICNB by using a validated method of standardized mean differences (SMDs) as described by Nguyen et al (9). The SMDs for these important prognostic variables will be reported in Table S1 (Supplemental material) and identified as potential imbalanced factors when the SMD exceeds 25%.

In Table 2, we will portray all details regarding the execution of the analgesic techniques including when it was performed (before, at the beginning, at the end or after the operation) and medication given (type, dosage and volume). For the TEA group we will report the test dose and continuous epidural mixture (local anaesthetics and opioids). The infusion rate (numerical in mL) from the time of placement until removal of the epidural catheter will be noted to calculate a total dosage (in milligram [mg] or microgram [ug]) of mixture given, reported as a continuous outcome. For the PVB group, the initial perioperative bolus given and the continuous infusion rate (in mL) until the day the PVB is stopped, will be recorded. For both TEA and PVB, also the number of days continuous infusion

was given will be noted. For the ICNB group the local anaesthetic given and the number of covered intercostal levels will be recorded. Any complication occurring during the execution of the analgesic technique will be reported in the text of the manuscript. Surgical and (general) anesthesia baseline characteristics will be shown in detail in Table 1.

Analysis

For appointing non-inferiority, both the ITT and PP will be performed and both should attain to the predetermined non-inferiority margin (the one-sided 98.65% CI upper bound of the difference in proportions not exceeding 17.5%). For superiority ($p<0.027$), the ITT analysis will be considered as the primary analysis and the PP as a supportive analysis. For secondary outcome measures, solely the ITT analysis will be performed.

Co-primary outcomes

Pain

Pain will be measured by the NRS score (0–10 scale, 0 meaning “no pain” and 10 meaning “the worst pain imaginable”) at 8 postoperative moments during POD 0 until 2. This outcome will be reported as the proportion of NRS measurements ≥4. The means of proportions per group will be reported with 95% CI. The upper limits of the 98.65% one-sided CI of differences in means of proportions for PVB versus TEA, respectively ICNB versus TEA, will be used to test for non-inferiority in the ITT as well as the PP analysis, represented in Figure 2 (2A and 2B).

Quality of recovery

QoR will be measured with the QoR-15 questionnaire at POD 1 and 2, and reported as the mean of these two values (Figure 2C). This outcome will be expressed as a discrete variable (minimum 0, maximum 150). Comparisons to test superiority will be made for the TEA versus PVB group and the TEA versus ICNB group. Superiority in terms of QoR is defined as a statistically significant higher mean score ($p<0.027$).

Secondary outcomes

During hospital admission after surgery, all secondary outcomes will be measured from POD 0 until POD 3 and if applicable, until discharge from the hospital (e.g. duration of chest tube drainage). The follow-up outpatient clinic visit is at 2-4 weeks after surgery, according to local hospital protocols. Outcomes are collected up until 30 days after surgery, as described in the protocol. All secondary outcomes will be compared between TEA versus PVB and TEA versus ICNB in the ITT group and tested for statistical significance ($p<0.027$). The data will be presented as illustrated in Table 3.

Pain scores during rest and mobilisation

Pain scores in rest and during mobilisation will be registered at: baseline (pre-operatively); at the recovery room and in the evening of POD 0; in the morning, afternoon, and evening of POD 1-3 and at the follow-up appointment, generating 13 moments in which the pain scores are prospectively measured. Since pain scores are repeated measurements from the same patient, they are likely to be correlated and we cannot assume independency. As we expect the effect of analgesia is patient-specific and will therefore vary substantially from patient to patient, a linear mixed model will be used (Figure 3a). This analysis will lead to a more precise estimate of the trend in pain scores and how this outcome changes over time per analgesic technique. The model will include random intercepts, and baseline scores, time of the measurement and treatment group as fixed effects. The

linear mixed model will accommodate unbalanced data patterns by assuming missing data at random and use all available observations and patients in the analysis (10). We will apply the covariance matrix that fits best according to Akaike's Information Criterion (AIC) (11).

Proportion of postoperative pain scores of NRS ≥ 4 during mobilization

Comparable to our co-primary outcome measure pain, the proportion of NRS measurements during mobilization ≥4 from POD 0 until 3 will be calculated by dividing the amount of NRS measurements ≥4 by the total amount of NRS measurements during mobilisation. Differences between randomization groups will be reported as percentages with 95% CIs and analysis will be done with a T-test or Mann-Whitney U test (Table 3).

QoR-15

The QoR-15 score ranges from 0-150 and will be expressed as a discrete outcome. Repeated measurements of QoR measured by the QoR-15 questionnaire taken at baseline (preoperative), from POD 0 until POD 3 and at follow-up will be analysed by a linear mixed model to depict the trend over time between the different analgesic techniques (Figure 3b).

Cumulative use of opioids and analgesics

Additional analgesics (paracetamol and non-steroidal anti-inflammatory drugs) and opioids are recorded per day, from POD 0 until 3. When possible, opioids will be converted to oral milligrams of morphine equivalents (MMEs) using the conversion table (12); if not possible (e.g. sufentanyl), opioids will be reported as a separate row (see Table 3). This outcome will be described as a

numerical continuous outcome in mg. Comparative analysis will be done with T-test or Mann-Whitney U test.

Postoperative complications

Postoperative complications are registered until 30 days after surgery and categorized according to the Clavien-Dindo (CD) classification (13). They will be pooled and analysed as minor complications (CD 1 and 2), major complications (CD 3 and 4) and mortality (CD 5). Comparisons will be done with Mantel-Haenszel chi-squared test or Fisher's exact test (Table 3).

Length of Hospitalization

Days of hospitalization will refer to the LOS after the anatomical lung resection, reported in whole nights as outcome measure. Differences between groups will be analysed with a Mann-Whitney U test (Table 3).

Patient satisfaction

Patient satisfaction is scored from POD 0 until 3 in a patient diary using a 5-point Likert scale (extremely dissatisfied, dissatisfied, neutral, satisfied, extremely satisfied). This categorical outcome will be analysed as with Mantel-Haenszel chi-squared test or Fisher's exact test (Figure 4a).

Presence of chest tube

The presence of the postoperative chest tube will be registered in whole nights during hospital admission as outcome measure with differences between the groups analysed with T-test or Mann-Whitney U-test (Table 3).

Presence of urinary catheter

The presence of a postoperative urinary catheter will be registered as whole nights in which the urinary catheter was present during hospital admission as outcome measure with group differences analysed with T-test or Mann-Whitney U-test (Table 3).

Degree of mobility

Degree of mobility was recorded in the patient diary using a 4-point Likert scale (only in bed, from bed to chair, from bed to the toilet, outside of the patient room). This categorical outcome will be analysed with Mantel-Haenszel chi-squared test or Fisher's exact test (Figure 4b).

Cost-effectiveness of analgesic techniques

The cost-effectiveness analysis will be conducted and published separately and is not included in this statistical analysis plan.

Patient replacement and missing data

In the sample size calculation, we have considered 12.6% extra inclusions due to drop-outs after conversions to thoracotomy (late exclusion). Since this percentage is appropriately represented by data from the Dutch Clinical Audit database from 2017, we do not expect further patient

replacement. Clinical data management is performed by independent professional data managers from the Dutch Comprehensive Cancer Centre. Once inclusions are complete, careful inspection of the data will take place. The mechanism causing data to be missing, whether it is (completely) at random or not at random, will guide the study group to apply analytical methods to amend missing data.

The incidence of missing data is partially limited by study design where minimum numbers of measurements suffice to generate an outcome value. For our non-inferiority research question regarding pain, complete cases include patients with at least 3 NRS measurements during POD 0 until 2 or a LOS ≤ 2 days, to allow detection of curvilinear pain patterns over time for reliable imputation. The cut-off for LOS ≤ 2 days is established due to the expectation that patients who have been discharged from the hospital have a NRS score ≤ 4 (standard of care). For our superiority question regarding QoR, complete cases include patients with at least one QoR-score during POD 0 until 2.

In case of remaining patients with lacking outcome data below 5% of the study size (14), the baseline Table 1 will be reproduced for patients intended to be included in the analysis as complete cases and added to the supplementary material (15). Imbalances in covariate distributions across groups derived from observed SMDs in this table, will be assessed from a clinical perspective for potential bias in prognosis and adjusted for in a primary analysis based on complete cases.

In case of remaining patients with lacking outcome data at or above 5% of the study size, the same procedure will be followed including a reproduced baseline table. In addition, missing data patterns will be studied to assess the likelihood of data being missing (completely) at random. If data are likely to be missing completely at random, multiple imputation (e.g. K-nearest neighbour imputation; multiple imputation by chained equation) and inverse probability weighting will be applied with presumably prognostic co-variates to substantiate the findings of the primary analysis. If data are likely to be missing at random, exploratory subgroup analyses will be run to restrict the target population for implementation of study results to the subgroups of patients closest to the observed

effect estimate in the complete case analysis. Restriction on the generalizability of study results will be fully reported in the supplementary material and discussed in the manuscript.

Additional analyses

Multiple regression of both co-primary outcomes will be done to explore and adjust for the impact of potential baseline imbalances (SMDs exceeding 25%). If opportune, adjusted contrasts between analgesic techniques will be reported.

Also, exploratory analyses will be done on primary and secondary outcomes per treatment centre (strata).

Harms

As described in the study protocol under "Adverse events and harms monitoring", the risk classification of the OPtriAL is scored as having negligible risk for study subjects. Moreover, there will be no new medicinal interventions, and all doses of applied anaesthetics are already used in daily practice. All adverse events per participant will be recorded until the end of the study and followed until they have abated, or until a stable situation has been reached.

Statistical Software

Analysis will be performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Armonk, NY) version 29.

OPtriAL study group

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Declarations

Ethics approval and consent to participate

This study is performed in accordance with the declaration of Helsinki, 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO, the Netherlands). The medical ethical committee of Utrecht University approved the study protocol (protocol number NL75375.041.20 version 02; METC-protocol number 20-787/D) and the amendment thereafter (version 03). In Belgium the medical ethical committee of the University Hospital in Antwerpen approved the study protocol (Project ID 20212021—0521—BUN B3002021000159). Prior to randomisation, written informed consent will be obtained from all participating patients.

Consent for publication

All participants have signed an informed consent which includes the consent for publication.

Data availability statement

The data that is originated from the OPtriAL study will be available through the FAIR principles (Findable, Accessible, Interoperable, and Reusable). The datasets and/or analysed data will be open access and available from the corresponding author on reasonable request. For a detailed data management plan, see our supplemental material Appendix C.

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References

(1) Spaans LN, Dijkgraaf MGW, Meijer P, Mourisse J, Bouwman RA, Verhagen, A. F. T. M., et al. Optimal postoperative pain management after VATS lung resection by thoracic epidural analgesia, continuous paravertebral block or single-shot intercostal nerve block (OPtriAL): study protocol of a three-arm multicentre randomised controlled trial. BMC surgery 2022 Sep 04,;22(1):1-330.

(2) Lim E, Batchelor TJP, Dunning J, Shackcloth M, Anikin V, Naidu B, et al. Video-Assisted Thoracoscopic or Open Lobectomy in Early-Stage Lung Cancer. NEJM evidence 2022 Feb 22,;1(3).

(3) Bendixen M, Jorgensen OD, Kronborg C, Andersen C, Licht PB. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. Lancet Oncol 2016 June 01;17(6):836-844.

(4) Feray S, Lubach J, Joshi GP, Bonnet F, Van de Velde M, Joshi GP, et al. PROSPECT guidelines for video-assisted thoracoscopic surgery: a systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia 2022 Mar;77(3):311-325.

(5) Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, Brunelli A, Cerfolio RJ, Gonzalez M, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). European journal of cardio-thoracic surgery 2019 Jan 01,;55(1):91-115.

(6) Spaans LN, Bousema JE, Meijer P, Bouwman RAA, van den Broek R, Mourisse J, et al. Acute pain management after thoracoscopic lung resection: a systematic review and explorative meta-analysis. Interdisciplinary CardioVascular and Thoracic Surgery 2023 Jan 04,;36(1).

(7) Campbell I. Chi-squared and Fisher-Irwin tests of two-by-two tables with small sample recommendations. Statistics in medicine 2007 Aug 30,;26(19):3661-3675.

(8) Busing, F. M. T. A., Weaver B, Dubois S. 2 × 2 Tables: a note on Campbell's recommendation. Statistics in medicine 2016 Apr 15,;35(8):1354-1358.

(9) Nguyen T, Xie L. Incomparability of treatment groups is often blindly ignored in randomised controlled trials – a post hoc analysis of baseline characteristic tables. Journal of clinical epidemiology 2021 Feb;130:161-168.

(10) Detry MA, Ma Y. Analyzing Repeated Measurements Using Mixed Models. JAMA : the journal of the American Medical Association 2016 Jan 26,;315(4):407-408.

(11) Chan YH. Biostatistics 301A. Repeated measurement analysis (mixed models). Singapore Med J 2004 October 01;45(10):456-461.

(12) Ju C, Wei L, Man KKC, Wang Z, Ma T, Chan AYL, et al. Global, regional, and national trends in opioid analgesic consumption from 2015 to 2019: a longitudinal study. The Lancet Public Health 2022;7(4):e335-e346.

(13) Dindo D, Demartines N, Clavien P. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004 August 01;240(2):205-213.

(14) Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. BMC Med Res Methodol 2017 -12;17(1).

(15) Groenwold RHH, Moons KGM, Vandenbroucke JP. Randomized trials with missing outcome data: how to analyze and what to report. CMAJ 2014 October 21;186(15):1153-1157.

Figure 1: . Enrollment, random assignment, and flow of study patients

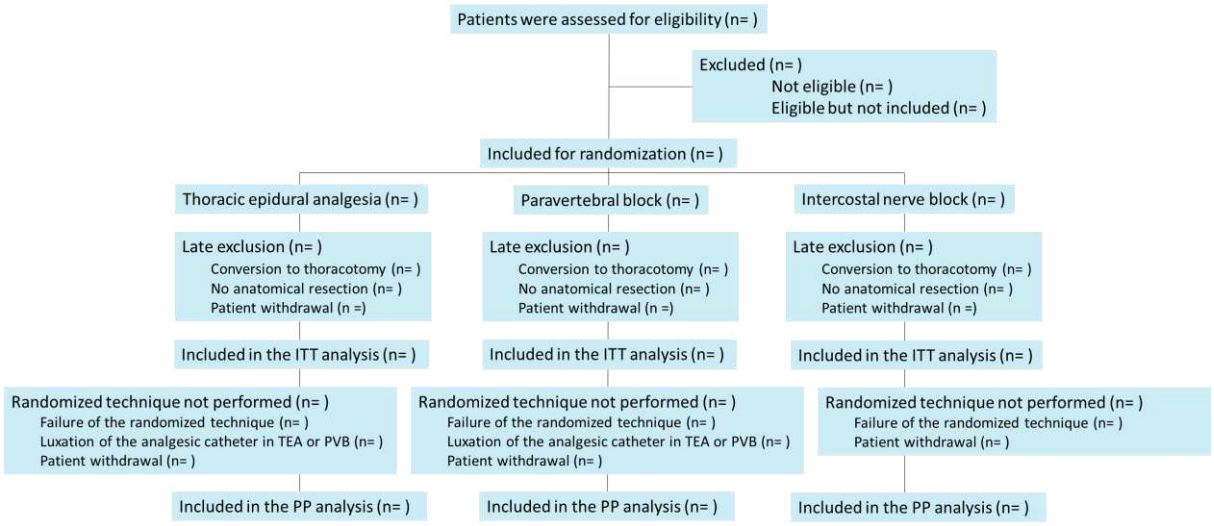
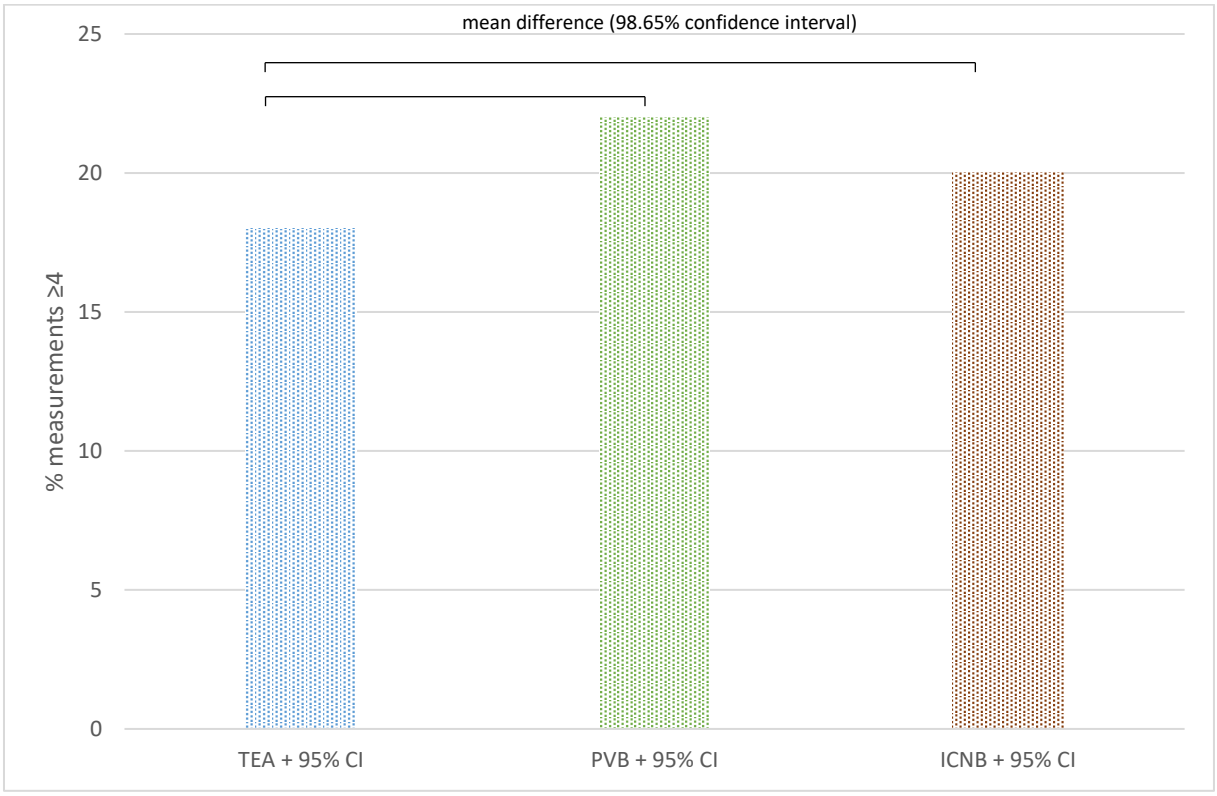
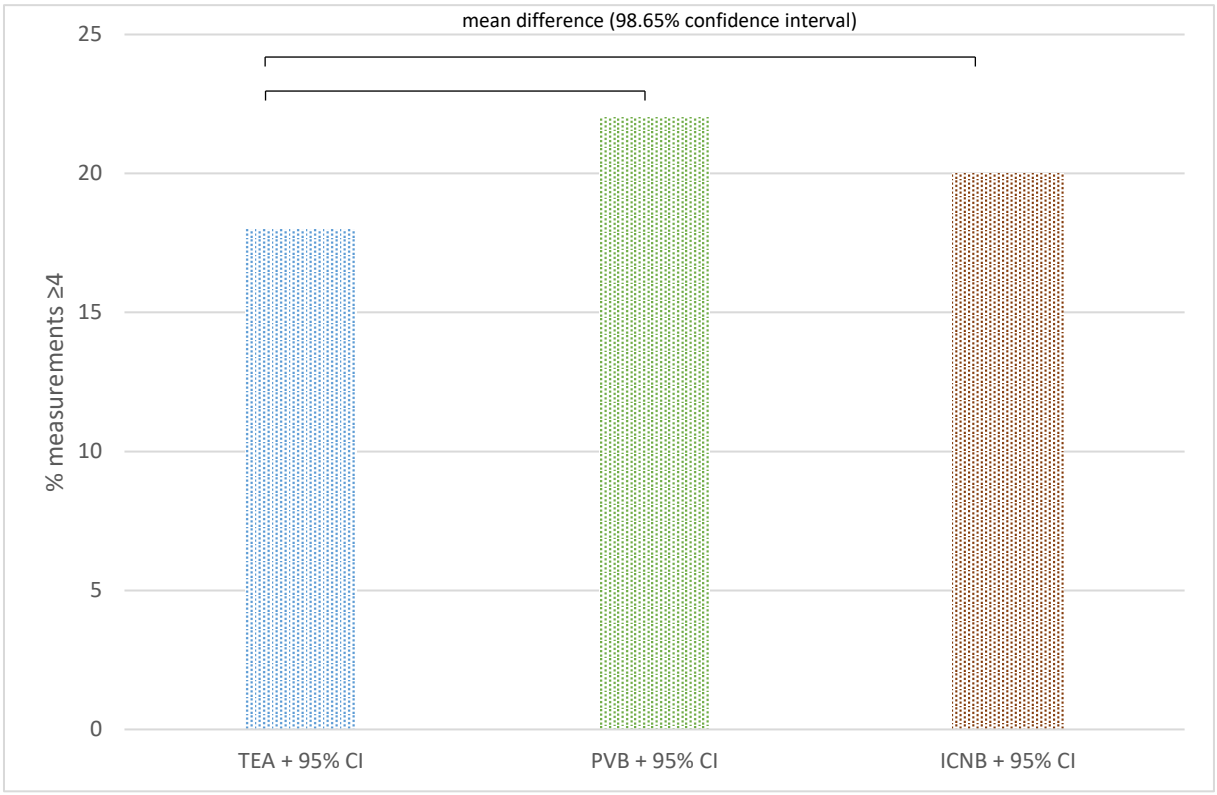


Figure 2: Graphical representation of the two co-primary outcomes (bar graphs with hypothetical data)

2A: Co-primary outcome pain, ITT population



2B: Co-primary outcome pain, PP population



2C: Co-primary outcome QoR, ITT population

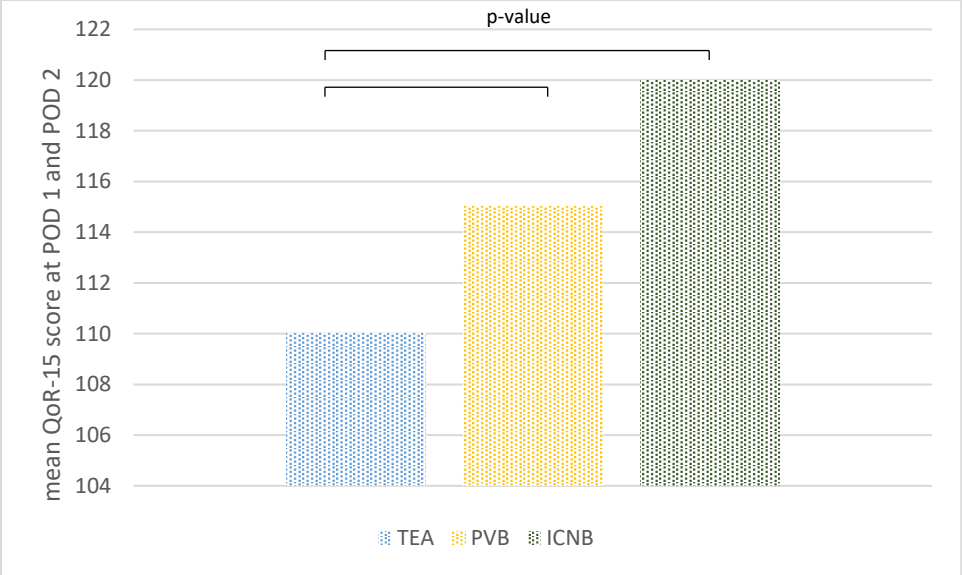
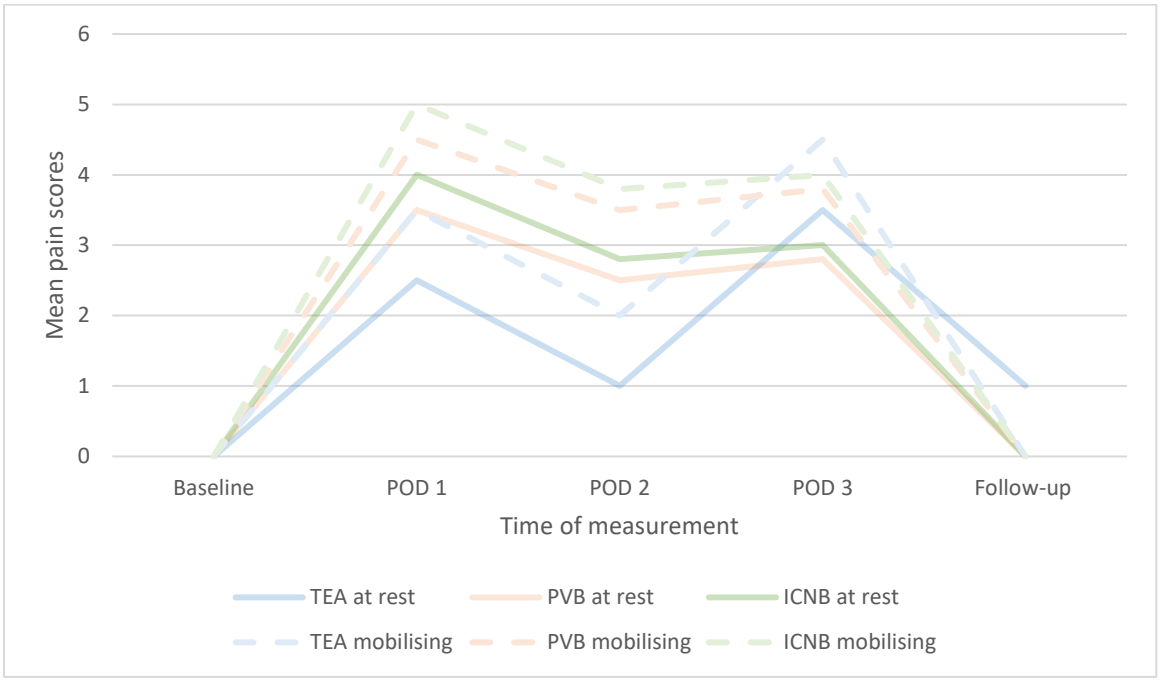


Figure 3:

3a. Linear mixed model for pain scores in rest and mobilizing from baseline, POD 0-3 and follow-up for each analgesic technique (lines represent hypothetical data)



3b. Linear mixed model for quality of recovery from baseline, POD 0-3 and follow-up for each analgesic technique (lines represent hypothetical data)

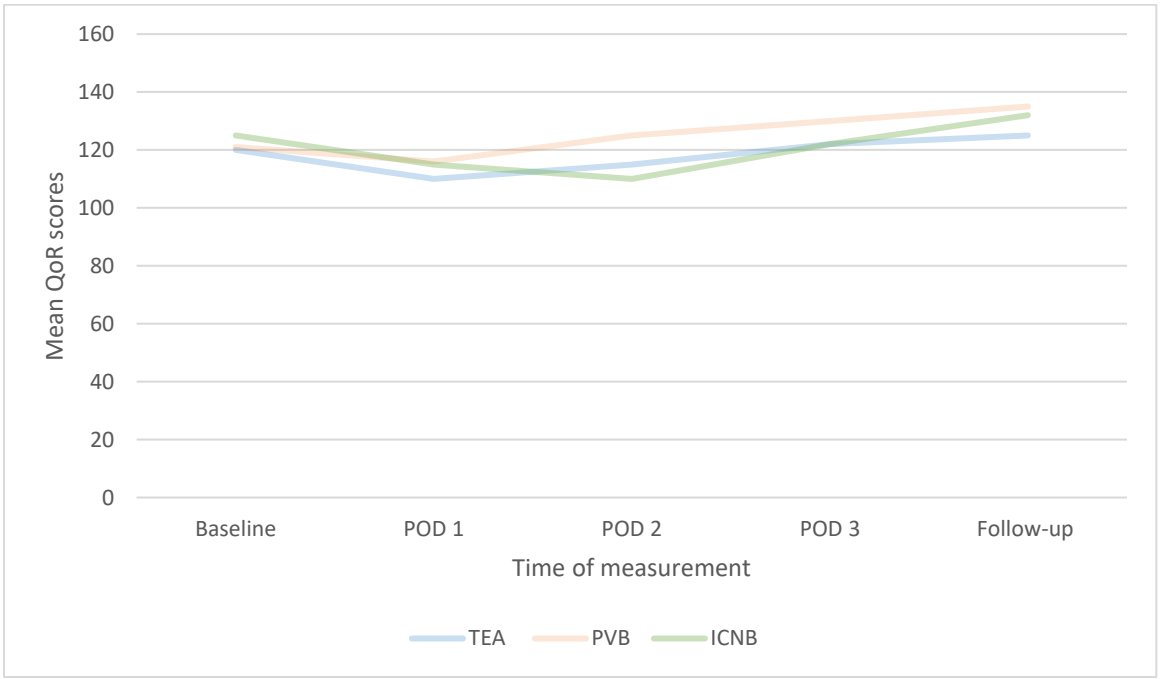
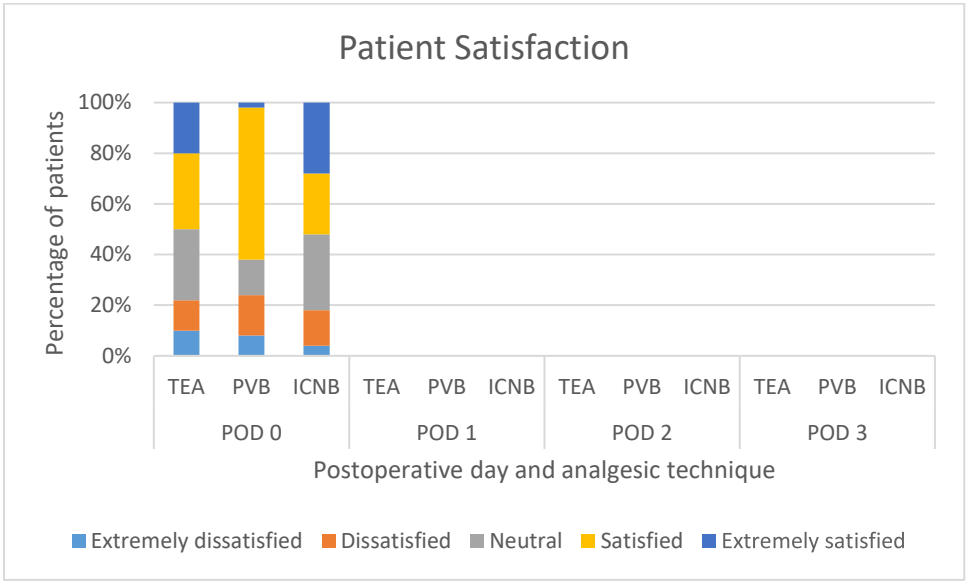


Figure 4: Generalized estimating equations for Patient Satisfaction and Mobility (including hypothetical data)

4a: Patient Satisfaction



4b: Patient mobility

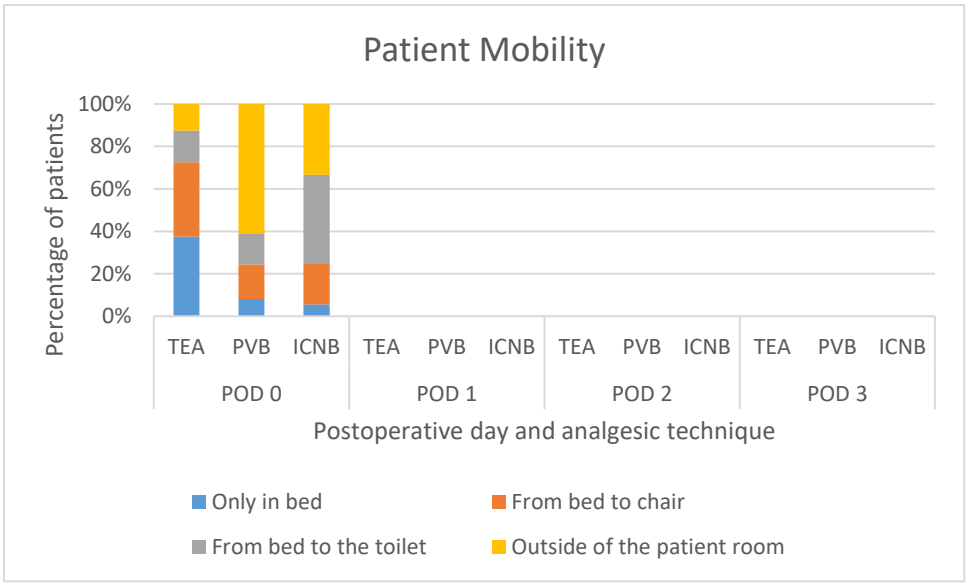


Table 1: Baseline patient, surgical and pain characteristics

Patient characteristics	**Thoracic Epidural Analgesia (N=)**	**Paravertebral block (N=)**	**Intercostal Nerve Block (N=)**
Age — yr			
Body-mass index			
Female sex — no. (%)			
Smoking status — no. (%)			
Smoker			
Non-smoker			
Ex-smoker			
WHO performance state — no. (%)			
WHO 0-1			
WHO 2-3			
WHO 4			
Comorbidities — no. (%)			
COPD (GOLD I, II, III and IV)			
Previous thoracic surgery/RXT			
Pain syndromes			
Psychiatric conditions			
Operation indication — no. (%)			
Primary lung cancer			
Metastasis			
Diagnostic			
Benign lesion			
Pathological TNM stage — no. (%)			
T1			
T2			
T3			
T4			
N0			
N1			
N2			
N3			
Baseline surgical characteristics			
Operation technique — no. (%)			
Uniportal VATS			
Multiport VATS			
Type of resection — no. (%)			
Segmentectomy(ies)			
Lobectomy			
Bi-lobectomy			
Pneumonectomy			
Operating time — min			
One chest tube — no. (%)			
Baseline anaesthesiology characteristics			
Pre-operative			
Analgesics — no. (%)			
Paracetamol			
NSAIDs			
Opioids			

Benzodiazepine — no. (%)	
Peri-operative	
Induction analgesia — no. (%)	
Propofol	
Benzodiazepine	
Opioids	
Muscle relaxant	
Local anaesthetics	
Sustained analgesia — no. (%)	
Propofol	
Benzodiazepine	
Opioids	
Muscle relaxant	
Local anaesthetics	
Dexamethasone — mg	
Antiemetic — no. (%)	
Vasopressives — no. (%)	

Plus–minus values are means ±SD. WHO denotes World Health Organisation, TNM denotes Tumor, Nodes and Metastasis, VATS denotes video-assisted thoracoscopic surgery, NSAIDs denotes non-steroidal anti-inflammatory drugs, NRS denotes numerical rating scale.
Body-mass index is the weight in kilograms divided by the square of the height in meters.
TEA: thoracic epidural analgesia; PVB: paravertebral block; ICNB: single-shot intercostal block; BMI: body mass index; No.: number; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; TNM: tumour nodes metastasis; VATS: video-assisted thoracoscopic surgery; NRS: numerical rating scale

Table 2: Performance of analgesic techniques

2A: Details regarding the execution of the thoracic epidural analgesia

Procedure TEA
Number of times executed
Preoperative placement — no. (%)
Placement by the anaesthesiologist — no. (%)
Test dose epidural given — no. (%)
Volume (mL)
Local analgesics given
Ropivacaine — no. (%)
Concentration ropivacaine (mg/mL)
Bupivacaine — no. (%)
Concentration bupivacaine (mg/mL)
Levobupivacaine — no. (%)
Concentration levobupivacaine (mg/mL)
Opioids given — no. (%)
Sufentanyl
Concentration sufentanyl (ug/ml)
Perioperative infusion rate — (ml/hour)
Postoperative infusion rate — (ml/hour)
Days in situ after operation — (days)

2B: Details regarding the execution of the paravertebral block

Procedure PVB
Number of times executed
Executed at the beginning of the operation — no. (%)
Executed by the lung surgeon — no. (%)
Bolus ropivacaine 7.5 mg/mL — no. (%)
Volume (mL)
Days in situ after operation (days)

2C: Details regarding the execution of the single-shot intercostal nerve block

Procedure ICNB
Number of time executed
Executed at the end of the operation — no. (%)
Executed by the lung surgeon — no. (%)
Local analgesic given
Ropivacaine — no. (%)
Concentration ropivacaine (mg/mL)
Bupivacaine — no. (%)
Concentration bupivacaine (mg/mL)
Levobupivacaine — no. (%)
Concentration levobupivacaine (mg/mL)
Total volume given (mL)
From thoracic level 2 to 10 — no. (%)

Table 3: Secondary outcome measures

Outcome	Thoracic Epidural Analgesia (N=)	Paravertebral block (N=)	p-value[1]	Intercostal Nerve Block (N=)	p-value[2]
Percentage of NRS≥4 during mobilizing POD 0-3					
Percentage of NRS≥4 at rest POD 0-3					
Analgesics and opioids at POD 0					
Paracetamol (mg)					
NSAID's (mg)					
Opioids (MME)					
Optional: opioids when MME not applicable					
Analgesics and opioids at POD 1					
Paracetamol (mg)					
NSAID's (mg)					
Opioids (MME)					
Optional: opioids when MME not applicable					
Analgesics and opioids at POD 2					
Paracetamol (mg)					
NSAID's (mg)					
Opioids (MME)					
Optional: when MME not applicable					
Analgesics and opioids at POD 3					
Paracetamol (mg)					
NSAID's (mg)					
Opioids (MME)					
Optional: when MME not applicable					
Postoperative complications — no. (%)					
CD 1 and 2					
CD 3 and 4					
CD 5 (mortality)					
Hospitalisation (days)					
Time to removal of chest tube (days)					
Presence of urinary catheter (days)					

Plus–minus values are means ±SD. NRS denotes numerical rating scale; POD denotes postoperative day; MME denotes milligrams of morfine equivalent; NSAIDs denotes non-steroidal anti-inflammatory drugs.CD denotes Clavien Dindo;
[1]p-value for the comparison between TEA and PVB; [2]p-value for the comparison between TEA and ICNB

Supplemental material

Inhoud

Table S1: Standardized mean differences for baseline characteristics of the ITT population

Patient characteristics	**Thoracic Epidural Analgesia (N=)**	**Paravertebral block (N=)**	**SMD[1]**	**Intercostal Nerve Block (N=)**	**SMD[2]**
Age — yr					
Body-mass index					
Female sex — no. (%)					
Smoking status — no. (%)					
Smoker					
Non-smoker					
Ex-smoker					
WHO performance state — no. (%)					
WHO 0-1					
WHO 2-3					
WHO 4					
Comorbidities — no. (%)					
COPD (GOLD I, II, III and IV)					
Previous thoracic surgery/RXT					
Pain syndromes					
Psychiatric conditions					
Operation indication — no. (%)					
Primary lung cancer					
Metastasis					
Diagnostic					
Benign lesion					
Pathological TNM stage — no. (%)					
T1					
T2					
T3					
T4					
N0					
N1					
N2					
N3					

Baseline surgical characteristics
Operation technique — no. (%)
Uniportal VATS
Multiport VATS
Type of resection — no. (%)
Segmentectomy(ies)
Lobectomy
Bi-lobectomy
Pneumonectomy
Operating time — min
One chest tube — no. (%)
Baseline anaesthesiology characteristics
Pre-operative
Analgesics — no. (%)
Paracetamol
NSAIDs
Opioids
Benzodiazepine — no. (%)
Peri-operative
Induction analgesia — no. (%)
Propofol
Benzodiazepine
Opioids
Muscle relaxant
Local anaesthetics
Sustained analgesia — no. (%)
Propofol
Benzodiazepine
Opioids
Muscle relaxant
Local anaesthetics
Dexamethasone — mg
Antiemetic — no. (%)
Vasopressives — no. (%)

SMD[1]: TEA versus PVB; SMD[2]: TEA versus ICNB. Plus–minus values are means ±SD. WHO denotes World Health Organisation, TNM denotes Tumor, Nodes and Metastasis, VATS denotes video-assisted thoracoscopic surgery, NSAIDs denotes non-steroidal anti-inflammatory drugs, NRS denotes numerical rating scale.

Body-mass index is the weight in kilograms divided by the square of the height in meters.

TEA: thoracic epidural analgesia; PVB: paravertebral block; ICNB: single-shot intercostal block; BMI: body mass index; No.: number; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; TNM: tumour nodes metastasis; VATS: video-assisted thoracoscopic surgery; NRS: numerical rating scale

Appendix A. Overview statistical test per outcome

Outcome	Planned statistical test to compare randomization groups (each intervention versus control)
Baseline characteristics	None*
Primary outcome	
% NRS ≥ 4 POD 0-2 (at rest)	Non-inferiority, upper limit 98.6% CI <17.5%
Mean QoR-15 POD 1-2	Unpaired t-test or Mann-Whitney U-test
Secondary outcomes	
% NRS ≥ 4 POD 0-2 (mobilization)	Unpaired t-test or Mann-Whitney U-test
% NRS ≥ 4 baseline, POD 0-3 and follow-up (at rest)	Linear mixed model
% NRS ≥ 4 baseline, POD 0-3 and follow-up (mobilization)	Linear mixed model
QoR-15 at baseline, POD 0-3 and follow-up	Linear mixed model
Cumulative use of analgesics POD 0-3	Unpaired t-test or Mann-Whitney U-test
Cumulative use of opioids POD 0-3	Unpaired t-test or Mann-Whitney U-test
Cumulative use of analgesics (including opioids) at follow-up	Unpaired t-test or Mann-Whitney U-test
Postoperative complications	Mantel-Haenszel chi-squared test or Fisher's exact test
Length of hospitalization	Mann-Whitney U-test
Patient satisfaction	Mantel-Haenszel chi-squared test or Fisher's exact test
Presence of chest drain	Unpaired t-test or Mann-Whitney U-test
Presence of urinary catheter	Unpaired t-test or Mann-Whitney U-test
Degree of mobility	Mantel-Haenszel chi-squared test or Fisher's exact test

Appendix B: Completed Checklist

Section/Item	Index	Description	Reported on page #
Section 1: Administrative information			
Trial and Trial registration	1a	Descriptive title that matches the protocol, with SAP either as a forerunner or subtitle, and trial acronym (if applicable)	1
	1b	Trial registration number	1
SAP Version	2	SAP version number with dates	3
Protocol Version	3	Reference to version of protocol being used	1
SAP revisions	4a	SAP revision history	N.A.
	4b	Justification for each SAP revision	N.A.
	4c	Timing of SAP revisions in relation to interim analyses, etc.	N.A.
Roles and responsibility	5	Names, affiliations, and roles of SAP contributors	1, 17
Signatures of:	6a	Person writing the SAP	1
	6b	Senior statistician responsible	1
	6c	Chief investigator/clinical lead	1
Section 2: Introduction			
Background and rationale	7	Synopsis of trial background and rationale including a brief description of research question and brief justification for undertaking the trial	4
Objectives	8	Description of specific objectives or hypotheses	4
Section 3: Study Methods			
Trial design	9	Brief description of trial design including type of trial (e.g., parallel group, multi-arm, crossover, factorial) and allocation ratio and may include brief description of interventions	4, 5, 6
Randomization	10	Randomization details, e.g., whether any minimization or stratification occurred (including stratifying factors used or the location of that information if it is not held within the SAP)	5
Sample size	11	Full sample size calculation or reference to sample size calculation in protocol (instead of replication in SAP)	6
Framework	12	Superiority, equivalence, or noninferiority hypothesis testing framework, including which comparisons will be presented on this basis	6
Statistical interim analysis and stopping guidance	13a	Information on interim analyses specifying what interim analyses will be carried out and listing of time points	7
	13b	Any planned adjustment of the significance level due to interim analysis	7
	13c	Details of guidelines for stopping the trial early	7
Timing of final analysis	14	Timing of final analysis, e.g., all outcomes analysed collectively or timing stratified by planned length of follow-up	7
Timing of outcome assessments	15	Time points at which the outcomes are measured including visit “windows”	7
Section 4: Statistical Principals			
Confidence intervals and *P* values	16	Level of statistical significance	7
	17	Description and rationale for any adjustment for multiplicity and, if so, detailing how the type 1 error is to be controlled	8
	18	Confidence intervals to be reported	Described for each outcome
Adherence and Protocol deviations	19a	Definition of adherence to the intervention and how this is assessed including extent of exposure	8, 9
	19b	Description of how adherence to the intervention will be presented	8, 9
	19c	Definition of protocol deviations for the trial	8, 9
	19d	Description of which protocol deviations will be summarized	8
Analysis populations	20	Definition of analysis populations, e.g., intention to treat, per protocol, complete case, safety	8, 9
Section 5: Trial Population			
Screening data	21	Reporting of screening data (if collected) to describe representativeness of trial sample	Figure 1
Eligibility	22	Summary of eligibility criteria	5, 9
Recruitment	23	Information to be included in the CONSORT flow diagram	Figure 1

Withdrawal/ Follow-up	24a	Level of withdrawal, e.g., from intervention and/or from follow-up	9
	24b	Timing of withdrawal/lost to follow-up data	12
	24c	Reasons and details of how withdrawal/lost to follow-up data will be presented	Figure 1
Baseline patient characteristics	25a	List of baseline characteristics to be summarized	Table 1
	25b	Details of how baseline characteristics will be descriptively summarized	Appendix A
Section 6: Analysis			
Outcome definitions		List and describe each primary and secondary outcome including details of:	
	26a	Specification of outcomes and timings. If applicable include the order of importance of primary or key secondary end points (e.g., order in which they will be tested)	11-15
	26b	Specific measurement and units (e.g., glucose control, hbA1c [mmol/mol or %])	11-15
	26c	Any calculation or transformation used to derive the outcome (e.g., change from baseline, QoL score, Time to event, logarithm, etc.)	11-15
Analysis methods	27a	What analysis method will be used and how the treatment effects will be presented	11-15, Appendix A
	27b	Any adjustment for covariates	11-15
	27c	Methods used for assumptions to be checked for statistical methods	8
	27d	Details of alternative methods to be used if distributional assumptions do not hold, e.g., normality, proportional hazards, etc.	8
	27e	Any planned sensitivity analyses for each outcome where applicable	11-15
	27f	Any planned subgroup analyses for each outcome including how subgroups are defined	11-15
Missing data	28	Reporting and assumptions/statistical methods to handle missing data (e.g., multiple imputation)	15, 16
Additional analyses	29	Details of any additional statistical analyses required, e.g., complier-average causal effect10 analysis	17
Harms	30	Sufficient detail on summarizing safety data, e.g., information on severity, expectedness, and causality; details of how adverse events are coded or categorized; how adverse event data will be analysed, i.e., grade 3/4 only, incidence case analysis, intervention emergent analysis	17
Statistical software	31	Details of statistical packages to be used to carry out analyses	17
References	32a	References to be provided for nonstandard statistical methods	18
	32b	Reference to Data Management Plan	Appendix C
	32c	Reference to the Trial Master File and Statistical Master File	
	32d	Reference to other standard operating procedures or documents to be adhered to	

Appendix C. Data management plan

Project Name: Optimal Postoperative Pain Management After Lung Surgery (OPtriAL)

Project Identifier: 10140021910007

Principal Investigator / Researcher: Frank van den Broek

Project Data Collector: Louisa Spaans

Funder: ZonMw (Netherlands)

Project and Data Collection Characteristics

1.1 Project Leader Contact Information

F.J.C. van den Broek

Máxima Medisch Centrum, Veldhoven, Surgeon, Department of Surgery

De Run 4600, 5504 DB, Veldhoven

Tel: 040-888-4110, Email: frankvanden.broek@mmc.nl

1.2 I have prepared my Data Management Plan (DMP) in collaboration with an expert in the field of data management. Please provide the name, position, organization/department, phone number, and email address of the expert.

• The expert is from outside my department/institution.

R.A. Scholte, Head of Data Management

Academisch Medisch Centrum Amsterdam, Clinical Research Unit, Head of Data Management

Meibergdreef 9, 1105 AZ, Amsterdam

Tel: 020-667649, Email: r.a.scholte@amc.nl

One year after the study's start, the researcher will evaluate the data management plan in consultation with the expert mentioned above. If necessary, changes will be made, and ZonMw will be informed accordingly.

1.3 When collecting data for my project, I proceed as follows:

• Use existing data (mention)

• Generate new data

Existing clinical data from the Electronic Patient Records (EPD) will be used, including age, gender, pain medication usage, tumor localization, tumor classification, and reports (surgery/pathology/anesthesia).

New data will be generated through questionnaires: pain scores, QoR-15 (Quality of Recovery-15), patient satisfaction, and postoperative mobility (assessed by a nurse or ward doctor).

1.4 I use the following within my research:

• Only quantitative data

The questionnaires related to pain, quality of recovery, opioid usage, mobilization, and comorbidities will be expressed as quantitative data. Additionally, the new data from the patient preference study will be structured and recorded as quantitative data.

1.5 I will reuse existing data and/or link to their data

• Yes, I have permission to use their data.

For the use of clinical EPD data, both patient (informed consent) and the primary physician (research contract) have given permission for use.

1.6 When collecting new data, I collaborate with other parties

• Yes, I collect new data in collaboration with other researchers, research groups (multicenter research).

Local researchers and IKNL (Netherlands Comprehensive Cancer Organization) data managers process the data through the electronic Case Report Form (eCRF) in Research Manager. Associated datasets are coded as SPSS files. Agreements regarding data accessibility, reusability, exchangeability, and auditability of (new) datasets, as well as ownership or co-production of data, will be documented in a research contract with each participating center and principal investigator.

1.7 I conduct the project in a consortium with two or more partners. Clear agreements have been made within the consortium regarding data management and intellectual property.

• Yes, clear agreements have been made regarding data management and intellectual property through a consortium agreement.

1.8 I can estimate the size of the data file, specifically the number of participants or subjects ("n=") in the data collection and the size in gigabytes/terabytes.

• Yes

Sample size calculation: n=450 patients, <1 GB of data.

1.9 I will make the following end products of the project available for further research and verification (briefly explain):

• (Various versions of) processed data

• Documentation about the data

• Documentation about the research process, including data from all involved parties

Processed data on which scientific articles are based. Raw data will be translated into different variables and provided in coded form. The codebook will indicate the codes for each variable. We will also report the data collection methods, the timing of questionnaire administration, how the questionnaires are scored, and how clinical data is coded. Due to privacy concerns, raw data will not be available for further research.

1.10 During the project, I have sufficient storage locations and capacity and have a data backup available. (Provide a brief explanation)

• Yes, I use my institution's standard facilities for data storage and backup.

Clinical data collection and storage are done using Research Manager. Local storage of the data after the data collection phase (processing and analysis), protocols, contracts, documents, and data processing software is on the secure drive of Máxima Medisch Centrum.

Legal and Regulatory Compliance (including privacy)

2.1 I will conduct human research and declare that I am aware of and comply with privacy-sensitive data regulations.

• Dutch Data Protection Act and the resulting Health Research Code of Conduct. I will register my project with the Dutch Data Protection Authority.

• Quality Assurance Human Research

• Dutch Act on Medical Research Involving Human Subjects (WMO). I will submit my project for review to a Medical Ethical Review Board.

• Dutch Medical Treatment Agreement Act

2.2 I will conduct human research and have arranged to obtain data with (a form of) participants' consent.

• Yes, please specify the form of consent.

• Yes, the form of consent allows data reuse.

Research contract signed per study site.

Research declaration signed by the local department heads of the study site.

Written informed consent from participants, granting consent for participation in this research (randomization, treatment, data analysis, completion of questionnaires, follow-up), and to reuse data and contact patients for follow-up research.

2.3 I will conduct human research and will anonymize or pseudonymize privacy-sensitive data.

• Yes, I will pseudonymize the data.

Patients will be assigned a code (e.g., OPtriAL-001), and the key code list will be kept by the local principal investigator and stored separately for potential future verification. Names and birthdates will not be used in the analysis.

2.4 I adhere to the privacy policy of the organization to which I am affiliated.

• Yes

Making Data Findable

3.1 The data collected in my project is findable for subsequent research. (Note: This is a core data that you must provide to ZonMw at the end of your project.)

• Yes, through the archive's (repository) search engine (please specify).

We will use an external archive, namely DANS.

3.2 I use a metadata standard for describing the data collection.

• No, I have not yet chosen a metadata standard.

The description of the data collection will be done using validated questionnaires. In the case of patient (clinical) data, the data will be described using a codebook.

3.3 I will use a Persistent Identifier (PI) to reference the data file in the long term.

• Yes, a DOI (Digital Object Identifier).

Making Data Accessible

4.1 After the project, the data will be accessible for verification and subsequent research.

• Yes, after an embargo period (explain)

Data will become available for non-commercial scientific research (open access) 12 months after the last data collection.

4.2 After the project, the data file will be publicly accessible without additional conditions (open access).

• No, I will impose conditions on data access (restricted access) (explain)

In collaboration with a legal expert from MMC, we have set a set of general conditions for data reuse. These can be found in the research contract with each study site.

4.3 I have usage conditions available to explain the terms of access to my data file after the project (provide a link or Persistent Identifier). (Note: This is a core data that you must provide to ZonMw at the end of your project.)

• No, my institution will establish usage conditions in collaboration with a legal expert.

4.4 In the conditions I impose on data usage (restricted access), I have included at least the checked points below.

• Conditions regarding data security

• Agreements on methodology

• Whether the dataset may be linked to another dataset (privacy)

• Sharing data for commercial purposes, taking into account state aid regulations

• Collaboration in dataset usage, including agreements on publications and authorships

• How the dataset will be made available

• The period of consent for dataset usage

• Approval of data requests will be decided by a steering committee, program committee, or project leader

• Participant consent allows follow-up research with the dataset

Data cannot be used for commercial purposes.

Making Data Interoperable

5.1 I choose a data format to make my data readable for other researchers and their computers ('machine actionable').

• Yes, specify.

SPSS file

5.2 I choose a metadata standard to enable my data to be linked to other data. (Note: This is a core data that you must provide to ZonMw at the end of your project.)

• No

There is no common metadata standard in our field. We use validated questionnaires, which are widely used in our field, and this approach will make the data interoperable. In the case of patient (clinical) data, the data will be described using a codebook.

5.3 I will conduct human research and have taken into account data reuse and potential linkage with other data files in privacy protection.

• Yes, participants have given consent for data reuse, and the data are pseudonymized.

Written informed consent

Making Data Reusable and Storing it Sustainably

6.1 I ensure good data quality and documentation so that other researchers can interpret and use them (a 'replication package').

• I document the research process (explain)

• I perform quality checks on the data to ensure completeness, correctness, and consistency (explain)

Data collection is done via Research Manager. An eCRF is entered by the IKNL data manager at each follow-up moment. Completeness checks are carried out by the research doctor working on the project.

External quality monitoring is conducted by IKNL. All centers are visited at the beginning and end of the study, and additional monitoring visits are conducted during the study based on high or low inclusion rates, data management queries, or other reasons leading the Principal Investigator to plan additional monitoring visits. At the end of the study, all centers will be visited by the research doctor.

6.2 I have selection criteria to determine which part of the data must be retained at the end of the project.

• Yes

All data will be retained for reproducibility. Depending on the end products in terms of reports and articles, the processed and used data will be stored.

6.3 At the end of the project, after data selection, I can estimate the size of the data file (in GB/TB) that I will store/ archive for the long term.

• Yes

Likely <1 GB gigabytes

6.4 I ensure that by the end of the project, I have chosen an archive or repository for the sustainable long-term archiving of my data file (certified).

• Yes, the archive has a data seal of approval (name the archive).

DANS (Data Archiving and Networked Services)

6.5 After the project, I will use the recommended minimum retention period of at least 10 years for my data.

• Yes (specify the number of years)

15 years according to the Dutch Act on Medical Research Involving Human Subjects (WMO) and Good Clinical Practice (GCP) guidelines.

6.6 The costs for data management during the project and data preparation for archiving are covered in the project budget.

• Yes (explain)

The costs are included in the budget submitted to ZonMw. The costs for local data management in a multicenter trial with a minimum of 10 participating centers, taking into account the protocol and Case Report Form (CRF), are estimated to be €128,458.05. Central data management, creation of a codebook, and an SPSS data file are tasks performed by the research doctor.

6.7 The costs of (data preparation for) archiving are covered.

• Yes (explain)

The costs for storing questionnaire data are covered by IKNL. The costs for storing clinical data in Research Manager are included in the license held by Máxima Medisch Centrum. The costs for storing local documents and data processing software are covered by Máxima Medisch Centrum.