RESEARCH PROTOCOL

Optimal postoperative Pain management After Lung surgery (OPtriAL): multi-centre randomised trial

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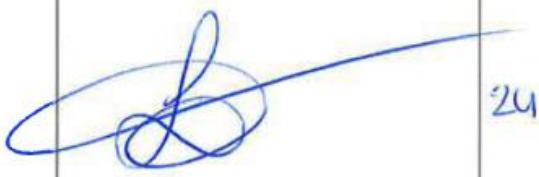
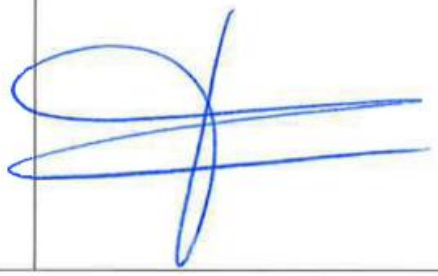
Head of Department: L.V.L. van Leeuwen Manager Department of Surgery Máxima Medical Centre, Veldhoven		24-11-20
Principal Investigator: F.J.C. van den Broek, MD, PhD, surgeon Department of Surgery Máxima Medical Centre, Veldhoven		26-11-20

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Events**
CRF	**Case Report Form**
ERATS	**Enhanced Recovery After Thoracic Surgery**
ICNB	**InterCostal Nerve Block**
NRS	**Numerical Rating Scale**
PIF	**Patient Information Folder**
POD	**PostOperative Day**
POS	**PreOperative Screening**
PVB	**ParaVertebral Block**
QoR-15	**Quality of Recovery-15 questionnaire**
RATS	**Robot Assisted thoracoscopic surgery**
SAE	**Serious Adverse Events**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
VATS	**Video Assisted Thoracic Surgery**
TEA	**Thoracic Epidural Anaesthesia**

1.0 Introduction and rationale

Adequate pain control after video-assisted thoracic surgery (VATS) for lung resection is important to improve postoperative mobilisation and recovery, and to prevent postoperative pulmonary complications. Thoracic epidural analgesia (TEA) is the usual care for postoperative pain management following thoracic surgery. Although the analgesic effect of TEA is clear, failure rates are 9-30% [1, 2, 3] and awake placement is stressful for patients. In addition, TEA is associated with patient immobilisation, bladder dysfunction and hypotension [4]. Based on the best available evidence and the recent guidelines by the Enhanced Recovery After Surgery (ERAS) society, the European Society of Thoracic Surgeons (ESTS) includes early mobilisation after surgery as one of their key recommendations [5].

The disadvantages of the TEA initiated the development of unilateral regional techniques for pain management. Single-shot and continuous paravertebral, intercostal, serratus anterior and erector spinae blocks have shown to be safe and effective [6]. A meta-analysis on single-shot versus continuous peripheral nerve blockade showed improved pain control, decreased need for opioids and greater patient satisfaction with the continuous infusion technique [7]. Another non-systematic review suggests poorer pain control in single shot techniques, however, this technique is easy to perform, has low costs compared to the standard TEA care [8] and lower incidence of adverse events [9]. Unilateral regional techniques are not associated with patient immobilisation, bladder dysfunction and hypotension [10].

So far, no consensus exists on optimal postoperative pain management after VATS lung resection. A review of enhanced recovery after thoracic surgery (ERATS) protocols strengthened the lack of unambiguity [11]. The five included protocols all used different techniques for postoperative pain management: oral, intravenous, intercostal, paravertebral and epidural anaesthesia. We conducted a systematic review and found that TEA resulted in mean pain scores of 1.8 (95%-CI 1.4-2.3) at 24 hours after surgery and 1.5 (95%-CI 1.2-1.8) after 48 hours. Continuous regional analgesia resulted in mean pain scores of 2.6 (95%-CI 1.9-3.5) and 2.1 (95%-CI 1.6-2.8) respectively, whereas single-shot regional analgesia resulted in mean pain scores of 2.2 (95%-CI 1.7-2.8) and 1.3 (95%-CI 0.9-1.7). Compared to a placebo control group, patients who received a single shot serratus plane block for VATS showed a superior quality of recovery during the first 2 days after the procedure. The postoperative analgesia was also improved in this group [12].

The Dutch Societies of Lung Surgery (NVvL) and Thoracic Surgery (NVT) provide no guidelines for postoperative pain management. The Dutch guideline database and the ESTS guideline on ERATS all address TEA as well as other regional techniques to be valid options for pain control after VATS. In January 2018, the NVvL introduced 2 of the 28 knowledge gaps of the Dutch Society of Surgery. The first addresses research on “optimal perioperative management after minimally invasive thoracic surgery”, which should finally lead to a Dutch ERATS protocol. Nationally, an ERATS working group is installed focusing on the disadvantages of TEA: hypotension, the need for a urinary catheter, immobilisation and stressful awake placement of the TEA catheter. There is much interest in the implementation of a multi-modal analgesic regimen without TEA and relying solely on single shot intercostal nerve block and systemic pain control. On the other hand, anaesthesiologists regard TEA as

the best current analgesic technique. A survey among Dutch lung and thoracic surgeons indeed pointed out that 69% of hospitals currently use TEA for pain control after VATS lung resection. The paravertebral block (PVB) provides a unilateral blockade of both somatosensory and sympathetic nerves. Therefore, next to TEA, PVB fits best in the concept of anaesthesiologists for pain control after VATS lung resection. Internationally, PVB has therefore gained much attention as a regional analgesic technique after VATS.

In addition to studying pain, patient satisfaction and postoperative quality of recovery (QoR) are crucial factors in the decision making of patient selected analgesic techniques. The 'Standardised Endpoints in Perioperative Medicine' (StEP) initiative seeks to provide guidance for researchers in their selection of patient-centred outcomes used in clinical effectiveness trials related to anaesthetic-specific interventions [13]. Quality of health is multidimensional and involves QoR as a whole, taking into account physical and mental well-being. Pain assessment continues to be a challenge due to its subjective nature and relation to various outcomes related to QoR, therefore, anaesthesia and pain studies strongly recommend using a patient related outcome measure reporting QoR to assess postoperative pain [14, 15]. To our knowledge, only two articles are published [12, 16] about pain and QoR after VATS using the QoR-40 item questionnaire. Recently, Stark and colleagues [17] developed a QoR-15 item questionnaire, which is proven to be an easy to use short version and is a validated and relevant tool for measuring QoR. The QoR-15 questionnaire contains the most relevant questions regarding physical and mental well-being after surgery and focuses on the following five domains: pain, physical comfort, physical independence, psychological support and emotional state.

1.1 Relevance for clinical practice

The results of the proposed study will impact guidelines to optimize perioperative care for VATS anatomic lung resection. Besides determining the most effective and efficient analgesic technique which meets patient's satisfaction, it will also determine the most cost-effective pain strategy and reduce variability in postoperative pain management that was found in a survey among surgeons in the Netherlands. When using TEA, patient immobilisation and indwelling urinary catheter usage may lead to prolonged hospital admission and infections. Reducing the length of hospital admission and morbidity, as well as eliminating the need of awake placement of TEA, may result in increased patient satisfaction.

Additionally, differences in costs among the different techniques may be found. We expect a cost reduction of €566 per patient per year when a paravertebral analgesic technique is used compared to TEA, and possibly a bigger cost reduction when ICNB is used. In case the PVB technique will be implemented in 84% of all Dutch patients (based on the response to a questionnaire sent) within 3 years after closure of the study, this will lead to a yearly reduction in costs of €1,267,048.

1.2 Implementation of the results

The results of this study will demonstrate which technique will be most cost-effective on postoperative pain management after VATS lung resection. Since perioperative management of minimally invasive surgery is mentioned as the most important knowledge gap by the NVvL and a national working group on ERATS has already been installed (including members

from both the NVvL and NVT), the results of this study will have direct impact on the advice that will be given by this working group. The principal investigator and professor A. Verhagen, co-applicant, are both members of the ERATS working group and have consulted the working group in advance of this study proposal with positive advice and acceptance of the results of this trial in the ERATS protocol.

Also European ERATS guidelines may be changed by this study. Publications will be submitted to high impact journals, preferably with open-access option. Our data will be searchable, accessible, interoperable, and stored in a sustainable manner. To achieve this, a data management plan will be made at the beginning of this project.

2.0 Objectives

The main objective is to compare regional continuous paravertebral block (PVB), single shot multi-level intercostal nerve block (ICNB) and thoracic epidural analgesia (TEA) as pain relief techniques in order to provide safe, effective and efficient pain management after thoracoscopic lung surgery. This study will provide the evidence for an ERATS protocol to be implemented for the optimal analgesic technique after VATS anatomic lung resection taking into account pain scores and QoR.

3.0 Study design

The proposed multi-centre randomised trial is a three-arm trial comparing PVB, single shot ICNB and TEA in a 1:1:1 ratio for pain (non-inferiority) and for QoR (superiority) in patients who have undergone a thoracoscopic anatomical lung resection. The CONSORT 2010 flow diagram is shown in Figure 1.

3.1 Hypothesis

Postoperative pain management by using either regional continuous PVB or single shot ICNB is non-inferior to TEA regarding pain in patients undergoing thoracoscopic anatomical lung resection. Regarding QoR after surgery the unilateral regional techniques are expected to be superior to TEA as scored by the global QoR-15 questionnaire. Signifying faster postoperative mobilisation, reduced morbidity and shorter hospitalization, these techniques may therefore reduce health care costs and improve patient satisfaction.

4.0 Study population

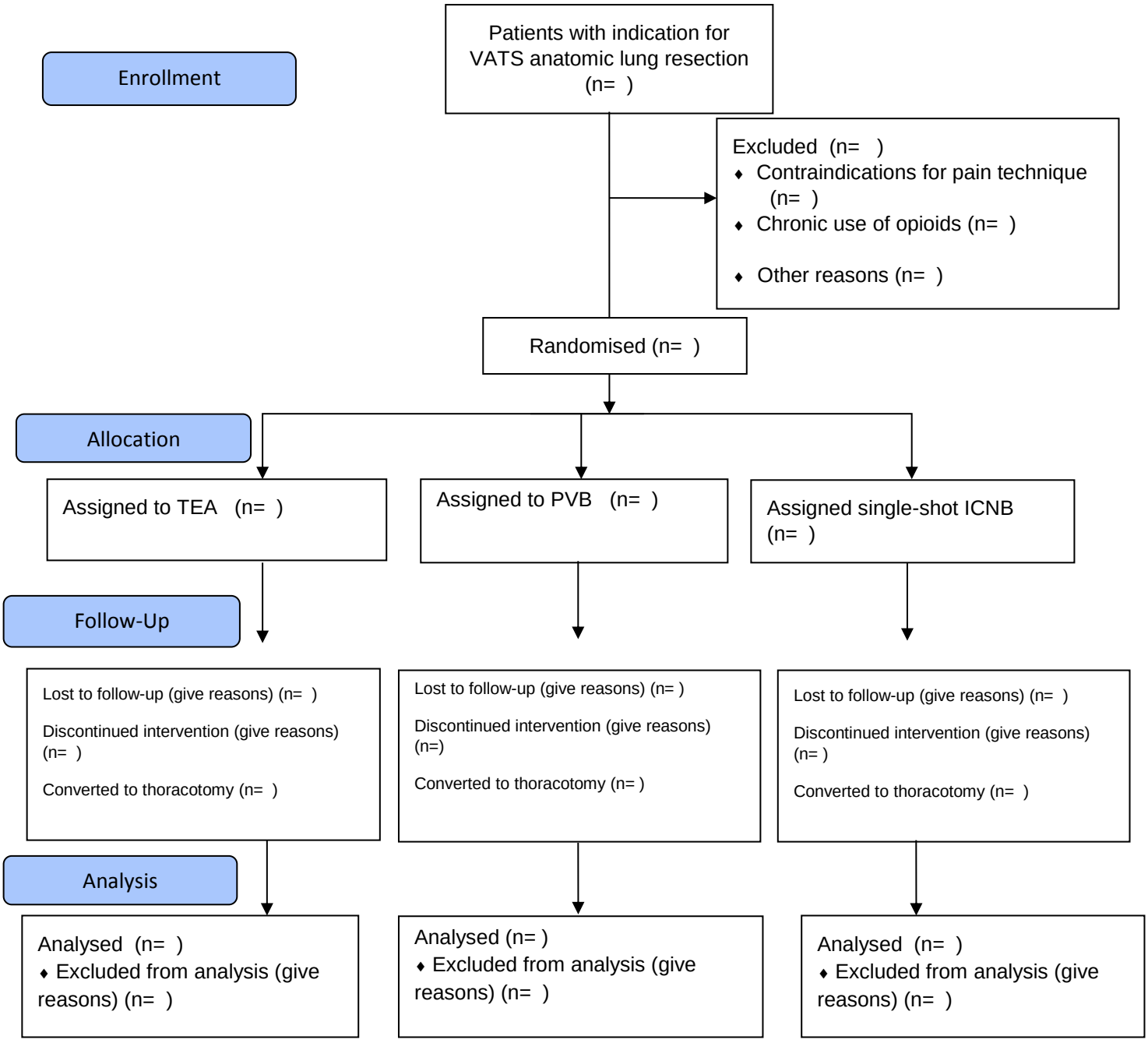
4.1 Population (base)

Patients referred for anatomical lung resection (pneumonectomy, (bi)lobectomy or segmentectomy) with the intention of performing it by VATS or RATS are eligible for the trial.

4.2 Inclusion criteria

Adult patients older than 18 years who are able to give informed consent and fill out questionnaires in Dutch.

Figure 1: CONSORT 2010 Flow Diagram



4.3 Exclusion criteria

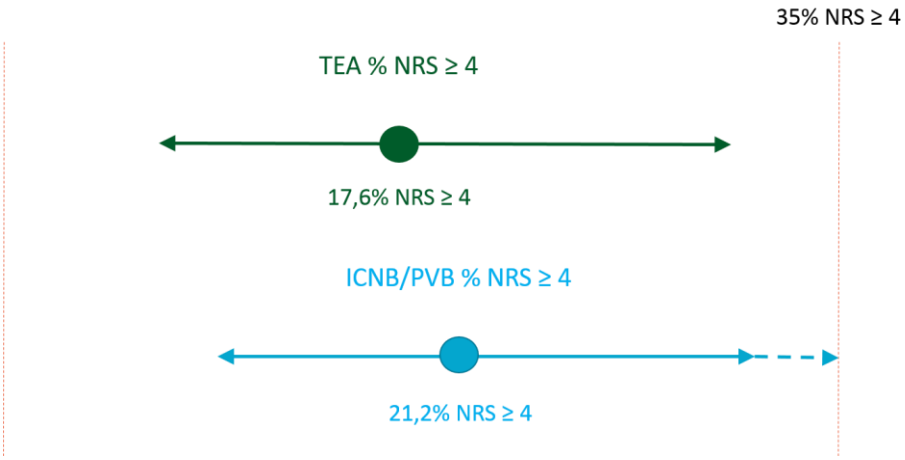
Patients with contra-indications for TEA or PVB (infection at skin site, increased intracranial pressure, non-correctable coagulopathy, bridging indication for therapeutic anticoagulation (CHADS-VASc ≥ 8), sepsis and mechanical spine obstruction) or allergic reactions to local anaesthetics will be excluded. Patients chronically using opioids for reasons not related to the operation will be excluded from the study since postoperative baseline opioid requirement will be higher and TEA remains the preferred technique for these patients. If, prior to the procedure, catheter placement during TEA is unsuccessful, a continuous PVB will be given during the procedure, and, if catheter placement during PVB is unsuccessful, a single shot multilevel ICNB will be used. Non-inferiority will be analysed based on intention-to-treat, as well as per-protocol analysis.

In case the lung surgeon estimates the operation to be performed through a thoracotomy technique instead of a VATS the patient will be excluded.

4.4 Sample size calculation

NRS ≥4 is clinically used as cut-off value above which patients have insufficient pain control. Therefore, a NRS ≥4 requires the nurse (or anaesthesiologist) to intervene and provide additional opioids. We believe this is a clinically significant step to determine adequate pain control or not. A previous pilot study performed by our group [18], comparing TEA (n=23) with subpleural continuous analgesia (n=23), as a unilateral regional continuous analgesia technique, showed 17.57% and 21.21% of the moments in which pain is measured patients had an NRS ≥4 at rest during POD 0-3, respectively. We as research group (lung surgeons and lung anaesthesiologists) find it clinically acceptable to increase the percentage of NRS ≥4 in the intervention group, in the worst case scenario, to 35% as upper limit of the 95% confidence interval (Figure 2). Since it concerns an upper limit, the actual percentage of patients with an NRS ≥4 will be somewhere between 17-35% that the study group finds acceptable, given the potential gain in QoR that is counterbalanced by it. We therefore accept an upper limit of 35.2% of measurements in the intervention group to have an NRS ≥4 to prove a clinically relevant non-inferiority margin.

Figure 2: Schematic overview non-inferiority margin



In case the patient indicates a NRS ≥4, additional opioids will be provided until adequate pain control is achieved. The effect of additional opioids will be consequently measured in the QoR-15 questionnaire. We calculated to include 167 patients in each randomization group to achieve a power of 90%, with alpha error of 0.025. Based on an assumed 12.6% drop-out rate due to conversion of VATS/robot assisted thoracic surgery (RATS to thoracotomy (Dutch Lung Cancer Audit data) we aim to include a total of 571 patients.

QoR-15 is reported to have a clinically relevant difference of 8.0 points with a standard deviation of 18 points [19]. Using this cut-off value for sample size calculation, the abovementioned sample size will be sufficient to determine superiority differences in QoR as well (power 100%).

5.0 Treatment of subjects

5.1 Preoperative analgesics

All patients will receive paracetamol (acetaminophen) 1000 mg. In addition, a non-steroidal anti-inflammatory drug (NSAID) will be given according to in house protocol unless contra-indications exist. All preoperative analgesics administered will be registered in the case report form (CRF).

5.2 General anaesthesia

For induction and maintenance of anaesthesia in house protocols will be used with the exception of lidocaine or esketamine which will not be administered during general anaesthesia. All patients will receive 8 mg dexamethasone to reduce additional postoperative opioid requirements and aid in the prevention of postoperative nausea and vomiting. In addition a 5HT3 receptor antagonist will be administered and additional anti-emetics based on risk factors and local protocols.

5.3 Intervention and usual care

5.3.1 Usual care (Group 1: TEA)

The epidural catheter will be placed in the awake patient after local anaesthesia of the skin. After correct placement of the epidural catheter, a local anaesthetic (ropivacaine, levobupivacaine or bupivacaine) will be started (at 7,5–20 mL/hour). According to in house protocols, an opioid will be added to the epidural solution. In the nursing ward, patients are allowed to mobilize under supervision when the motor function and sensibility of the extremities allows it. A provisional stop of the administration of the epidural infusion is planned after 48 hours (on the second postoperative day). In case NRS pain scores are ≥4 despite additional pain medication, the TEA will stay in place and the epidural infusion is resumed after a bolus of 5 mL of the epidural infusion. After administration of the epidural infusion bolus, the vital signs of the patient are controlled for at least 30 minutes. Subsequently, NRS pain scores will be assessed daily until pain management is sufficient and the TEA can be withdrawn with a maximum of 4 days. If rescue attempts to the epidural anaesthesia fail to improve pain scores, opioids may be withdrawn from the epidural solution and oral or intravenous opioids will be supplied.

In case an accidental spinal puncture during placement of the TEA catheter occurs, the patient is not considered eligible for the TEA technique. In this case, the same measures will

be applied as stated under 4.3 Exclusion Criteria, thus: a PVB catheter is placed instead (see Figure 3).

5.3.2 Interventions

5.3.2.1 Group 2: continuous regional PVB

The PVB catheter is placed after general anaesthesia at the beginning of the VATS/RATS procedure under direct thoracoscopic vision. If placement cannot be achieved at the beginning of the operation as a result of poor thoracoscopic vision the catheter will be placed at a later stage or at the end of surgery. It is strongly preferred to place the PVB at the beginning of the VATS procedure to benefit from the advantages of administering local anaesthetics from the beginning of the operation. If the PVB is placed at the end of the procedure, patients will need more intravenous opioids during the operation which can interfere with reliable data collection of pain scores and opioid use in the recovery room.

In order to place the PVB catheter, identify the paravertebral space (an additional option is to use the thorax CT scan for an overview of the landmarks) with the following landmarks: the height of the paravertebral block is at T4-T5 or T5-T6 (carina height), 2-3 cm lateral from the midline (processus spinosus) and 3-6 cm of depth measured perpendicularly from the skin. After induction of anaesthesia the patient is positioned in lateral decubitus and the relevant landmarks are identified. Optionally, placement of the PVB catheter can be achieved with the aid of ultrasonography. For this, start laterally from the vertebral column and identify the rib and the pleura. Move medially and identify the processus transversus. Locate the middle between two processus transversi and mark the puncture site. Under thoracoscopic vision, identify the sympathetic chain. In all cases the surgeon will identify the paravertebral space under thoracoscopic vision. A Tuohy needle is inserted at the before mentioned marked location. After feeling a “fascial pop” penetrating the intercostal ligament, feel the loss of resistance when entering the subpleural space. At the same time, observe the appearance of the needle tip under the pleura thoracoscopically. Once the needle is placed in the paravertebral space, place a syringe with ropivacaine 7.5mg/mL and create hydrodissection with a minimal amount (2 cc) of ropivacaine to reach the adequate paravertebral plane for placement of the catheter. Insert the catheter under thoracoscopic vision. Remove the Tuohy needle while maintaining the catheter in place and the catheter lays next to the sympathetic chain under direct thoracoscopic vision. Join the connector to the catheter and inject a bolus of local anaesthetic of 15-20 mL ropivacaine 7.5 mg/mL or levobupivacaine 2.5 mg/mL. Ensure fixation of the catheter to the skin by using a fixation plaster.

A ropivacaine 2 mg/mL pump for continuous infusion is given with an infusion rate of 4-10ml/hour, in case of insufficient pain control (NRS ≥4) a bolus of 4-5 mL is given (in case a patient controlled (epidural) anaesthesia pump is available with a lockout of 20 minutes). No opioid additives or opioids will be administered through the paravertebral catheter. A provisional stop of the administration of local anaesthetics is planned on the second postoperative day after which removal is considered based on the effect on pain intensity, comparable to the TEA group. No mobility restrictions are needed in this group.

5.3.2.2 Group 3: single shot ICNB

At the end of the surgery a single shot ICNB will be placed at 6 levels (T3-T8) with bupivacaine 2.5 mg/mL or levobupivacaine 2.5mg/mL and 2-3mL per site under direct thoracoscopic vision. The injection site will be chosen in the intercostal space, just lateral adjacent to the sympathetic trunk. This group will have no analgesic catheters for continued analgesia with local anaesthetics. No mobility restrictions are needed in this group.

5.5 Escape medication

If following awakening from anaesthesia in the recovery room the patient experiences inadequate pain control (NRS ≥ 4) and a bolus of epidural infusion via de epidural catheter or local anaesthetic via the paravertebral catheter is insufficient, intravenous morphine will be given until a maximum dose specified by the attending anaesthesiologist. If insufficient pain control is achieved, additional clonidine 1 µg/kg or esketamine (depending on patient's hemodynamics and local protocol) is injected intravenously in order to obtain adequate pain control (NRS <4). If the above regime does not result in adequate pain control additional interventions will be administered at the discretion of the attending anaesthesiologist. All analgesic medications and interventions given will be registered in the CRF.

5.6 Postoperative medication

The following medication will be provided to each patient: paracetamol (acetaminophen) 4 times a day 1000 mg, NSAID according to in house protocols and oxycodon 6 times a day 5 mg as needed. If this regime does not provide adequate pain control, additional opioids will be provided either orally (slow release) or intravenously by patient controlled analgesia. The latter can either be initiated in the recovery room or on the nursing ward. All analgesic medications and interventions will be registered in the CRF.

5.7 Accidental removal (luxation) of the catheter on the ward

In case the placed TEA or PVB catheter is accidentally removed in a non-surgical setting, for example on the nursing ward or the recovery room, the patient will be given systemic analgesia at discretion of the attending anaesthesiologist. This is not a reason for exclusion of the patient (Figure 2).

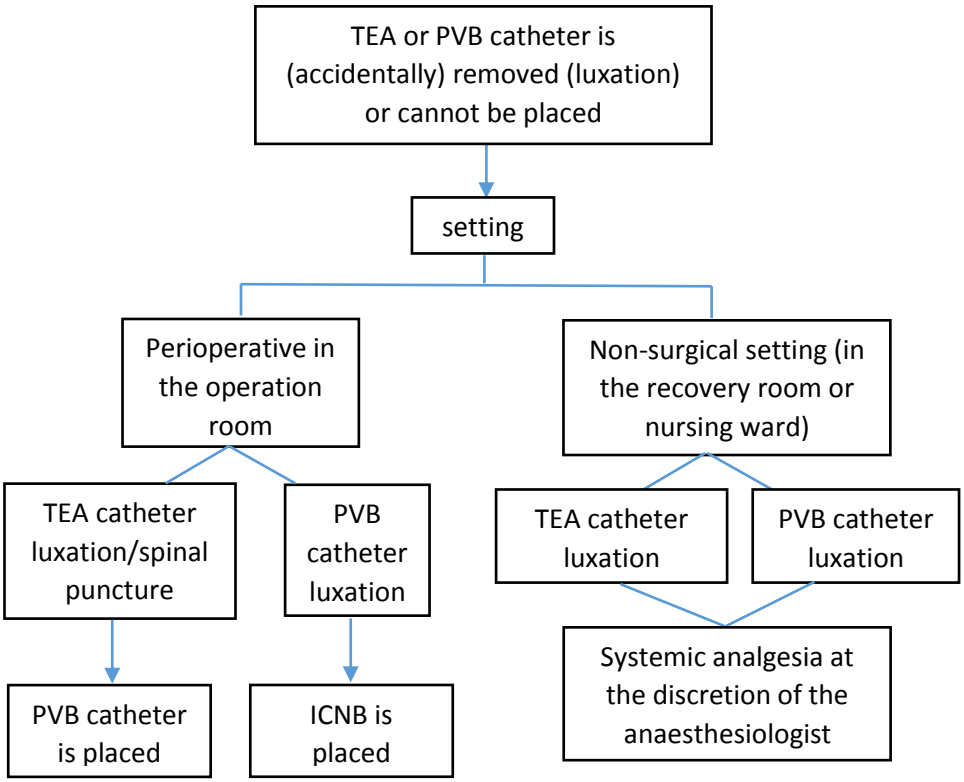
6.0 Investigational product

Not applicable

7.0 Non-investigational product

Not applicable

Figure 3. Decision making in case a TEA or PVB catheter is accidentally removed or cannot be placed



8.0 Methods

8.1 Study parameters/endpoints

Mean pain score expressed on a numerical or visual analogue scale is the most used outcome in studies focusing on postoperative pain after VATS. The subjective nature of this outcome measure and its extensive use in the existing literature without leading to concrete changes in anaesthetic care triggered our study group to re-establish its significance and look for an improved outcome parameter. Inadequate pain control is a distressing situation and when present, stimulates the health care worker to take action. In the clinical setting action is taken when the patient presents with a NRS ≥4. Therefore, the proportion of episodes with a NRS ≥4 as primary outcome parameter represents a clinically relevant outcome to define and measure pain.

Furthermore, to ensure a wide implementation of the results and a patient's perspective when studying pain techniques to improve postoperative recovery, the QoR-15 is a validated and highly relevant questionnaire to take into account as primary outcome measure [19, 20,21].

Looking into the optimal pain management after lung surgery has a direct relationship with the quality of recovery after lung surgery. Optimal pain relief is important on the one hand for the immediate well-being of the patient, and on the other hand for an enhanced recovery after surgery. A potential disadvantage of optimal (that sometimes means additional) pain relief is delay in recovery and a lowering of the quality of recovery (due to,

for example, side effects of additional pain relief, immobilization, urinary catheter use, fear of inserting catheters, etc.). We make a trade-off between more moments of pain with a NRS ≥4 versus a better quality of recovery based on the QoR-15 score.

It should be noted here that patients who report a pain score of 4 or higher are offered additional pain relief to lower the pain score again. This extra pain relief is of course registered and may also have consequences for the quality of recovery as explained above (e.g. more side effects due to opioids, which may lower the 'Quality of Recovery' score).

8.1.1 Main study parameter/endpoint

The NRS (0-10; 0= no pain, 10=worst imaginable pain) will be used to measure pain scores. The primary outcome measure for 'non-inferiority' is the proportion of NRS ≥4, defined as the number of NRS ≥4 episodes divided by the total amount of NRS pain scores obtained. A minimum of 11 NRS pain scores will be collected (at the recovery room (1), on the ward (10)). The primary outcome for 'superiority' is QoR measured with the QoR-15 questionnaire on POD 1 and POD 2. The QoR-15 will provide a continuous variable with a minimum score of 0 and maximum score of 150, and contains the most relevant questions concerning 5 domains (emotional status, physical comfort, psychological support, physical independence and pain) of overall well-being and recovery after surgery.

8.1.2 Secondary study parameters/endpoints

1) Pain scores during rest and mobilisation at baseline, in the morning, afternoon and evening on POD 0-3 and at 2-3 weeks follow-up;

2) Proportion of postoperative pain scores of NRS ≥4 during mobilization at POD 0-3;

3) QoR-15 pre-operatively (baseline), POD 0, POD 3 and at 2-3 weeks follow-up;

4) Cumulative use of systemic opioids and analgesics at POD 0-3;

5) Postoperative complications until 2-3 weeks follow-up, according to the Clavien-Dindo classification;

6) Hospitalization, defined as the total number of days in hospital after the surgical intervention (including readmissions within the first 30 postoperative days). The following standardised discharge criteria after surgery will be applied in all participating hospitals: normal intake of nutrition; independent mobility; absence of fever (<38 °C); and no presence of chest tube.

7) Patient satisfaction (5-point Likert scale: not at all satisfied, slightly satisfied, neutral, very satisfied and extremely satisfied);

8) Time to removal of thorax drain in days;

9) Time to removal of urinary catheter in days;

10) Degree of mobility (1-4 scale: on the bed (1), to the chair (2), to the toilet (3), outside the patient's hospital room(4));

11) Cost-effectiveness of analgesic techniques from a health care perspective (see paragraph 10.3.1 'Economic Evaluation');

8.1.3 Other study parameters

Not applicable

8.2 Randomisation, blinding and treatment allocation

8.2.1 Randomisation

After informed consent, provided during the preoperative appointment with the lung surgeon at the outpatient clinic, patient data are entered into a computerised database (Research Manager) and with an unchangeable computer generated number patients will be randomised (1:1:1) for one of the three analgesic strategies.

All included hospitals use the Dutch ERATS protocol for the entire postoperative period, as a result of which only the randomised analgesic strategy will differ among patients.

As local anaesthesiology protocols may slightly differ between hospitals regarding type of NSAIDs and general anaesthesia, and slight differences may exist in usage of uniportal or multiportal VATS, randomisation will be stratified by treatment centre in randomised blocks.

To the best of our knowledge, pain and QoR related to lung surgery are not directly influenced by secondary factors such as age, gender, disease stage or surgical approach (pneumonectomy, lobectomy or segmentectomy) [23, 24, 25, 26,27]. Therefore, these factors do not require stratification.

8.2.2 Blinding

As the analgesic strategies highly differ in nature (with or without percutaneous catheter) and/or postoperative care (mobility with or without prerequisites, urinary catheter placement), blinding for the randomised strategy is unfeasible.

8.2.3 Treatment allocation

After randomisation, the patient will be scheduled for either a TEA, PVB or single shot ICNB. After the preoperative outpatient clinic appointment with the surgeon, the patient is scheduled for a preoperative screening (POS) at the department of anaesthesiology. When the patient presents themselves at the POS, the anaesthesiologist will have knowledge of the randomised technique in which the patient was allocated. At this point, the anaesthesiologist will inform the patient about the technique that is going to be applicable at the time of the operation, as well as the risks and benefits of the technique (standard routine).

8.3 Study procedures

A detailed description of the study procedures in the usual care and intervention groups of this study are provided in chapter 5.0. The study subjects will be randomised into three groups and will receive either the usual care (TEA) or will be allocated to one of the intervention groups (PVB or ICNB). Before, during and after the intervention is given, patients will be asked to fill in a number of assessments concerning the study end points. A detailed overview is shown in the schedule of assessments (Table 1).

Table 1. Schedule of assessments

Assessment	Indication for VATS anatomical resection after multidisciplinary meeting	Baseline (Pre-operative outpatient clinic consultation)	Day 0 (day of the operation)	POD* 1	POD 2	POD 3	Hospital discharge	Postoperative outpatient clinic consultation (2-3 weeks after operation)
Time point	t-1	t0	t1	t2	t3	t4	t5	t6
Assessment of eligibility	X	X**						
Written informed consent		X						
NRS pain score at rest		X						X
Morning				X	X	X		
Afternoon			X	X	X	X		
Evening			X	X	X	X		
NRS pain score during movement		X						X
Morning				X	X	X		
Afternoon			X	X	X	X		
Evening			X	X	X	X		
QoR-15 questionnaire		X	X	X	X	X		X
Dosage use of opioids and analgesics			X	X	X	X		
Patient satisfaction			X	X	X	X		
Postoperative complications							X	X
Patient mobility			X	X	X	X		
Hospitalization ***								X
iMTA - iMCQ		X						X
iMTA - iPCQ		X						X

*POD: postoperative day

** Assessment of eligibility can take place during a multidisciplinary meeting or can take place if the patient is referred to the surgeon for anatomical resection without a multidisciplinary meeting beforehand.

*** Readmission within 30 days after surgery

8.4 Withdrawal of individual subjects

Study subjects always have the possibility to withdraw from the study. There are no predefined criteria for withdrawal of study subjects. In case subjects withdraw from the study after informed consent has been given, the reason will be asked and reported. In case no reason is given, this will be reported.

8.4.1 Specific criteria for withdrawal

There is no specific criteria for withdrawal.

Late exclusion of study subjects will be applicable in case of thoracotomy and/or patient related cessation of the analgesic technique for which the patient was randomised. Therefore, we include an intention to treat and per-protocol analysis in the statistical analysis.

8.5 Replacement of individual subjects after withdrawal

In our sample size calculation (see paragraph 4.4), we assumed a 12.6% drop-out rate due to conversion of VATS to thoracotomy. Therefore we will not replace individual subjects after withdrawal, unless drop-out rate exceeds 12.6%. In this case, patients will be added in order to reach 501 patients for the final analysis.

8.6 Follow-up of subjects withdrawn from treatment

In case subjects withdraw from study participation before the operation, these patients will undergo treatment and follow-up according to local treatment and follow-up protocols. These individuals will be asked for permission to just register their information on actual treatment and regular follow-up, in order to report outcome of withdrawn cases.

8.7 (Premature) Termination of the study

The studied interventions in which study subjects will be randomised are not experimental and are already being used (inter)nationally. According to a survey we conducted among thoracic surgeons and anaesthesiologists in the Netherlands in 2019 asking about the preferred analgesic technique used during VATS anatomic lung resection; 69% performed a TEA, 5.4% used a PVB and 18.2% used an ICNB. Therefore, we expect the interventions will not lead to unexpected events leading to premature study termination.

9.0 Safety reporting

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The coordinating investigator will take care that all subjects are kept informed.

As no interim analysis is planned, a temporary halt is not expected. As the intervention groups in our study are already implemented in most participating centres.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the intervention. All adverse events and serious adverse events (SAEs) will be scored according to the Clavien-Dindo classification:

- Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic or radiological interventions
- Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
- Grade III: Requiring surgical, endoscopic or radiological intervention.
- Grade IV: Life-threatening complication (including CNS complications) requiring Intensive Care management
- Grade V: Death of a patient

The primary end point of the study will be reached 2-3 weeks after lung surgery. We will record all AEs during the first 30 days after surgery.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a SAE.

The investigators will report all SAEs to the sponsor/coordinating investigator without undue delay after obtaining knowledge of the events, except for the following SAEs, that will be registered and reported each half year to the medical ethical committee (METC):

- Regular postoperative complications after anatomic surgical resection (e.g. segmental resection, (bi)lobectomy or pneumonectomy): wound infection or dehiscence, bleeding, prolonged postoperative air leakage >5 days, pneumonia, atelectasis requiring bronchoscopy, urinary tract infection, thoracic empyema, thromboembolic events and cardiac arrhythmias.

- Complications related to the study groups (TEA, PVB and ICNB): infection at the site of injection and post-puncture spinal headache.

The local investigators are responsible for reporting SAEs. All SAEs, whether or not considered to be related to the study treatment, must be reported by e-mail to louisa.spaans@mmc.nl within 24 hours, using the completed SAE report form. The sponsor/coordinating investigator will report the concerning SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported

within a period of maximum 15 days after the sponsor/coordinating investigator has first knowledge of the SAEs.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable since no new medicinal products are being investigated.

9.3 Annual Safety Report

Not applicable since no new medicinal products are being investigated.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported until end of study, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB)

According to the risk classification the OPtriAL has negligible risk for the study subjects. Therefore, there is no need for a DSMB. The intervention techniques do not possess extra safety risks or complications compared to the control group. All patients, regardless of the randomisation group, will have monitoring of vital parameters and direct presence of experts in the field if required. Moreover, there will be no new medicinal intervention and all doses of applied anaesthesia through the catheters are already used in daily practice. See paragraph 11.4.

10.0 Statistical analysis

10.1 Primary study parameters

The proportion of postoperative pain scores of NRS ≥4 at rest will be presented as percentages with 95% confidence interval (95-CI) and QoR-15 questionnaire scores (maximum 150 points) will be presented as means with standard deviation or median with interquartile range depending on distribution. Comparisons will be made by the chi-squared test and student's t-test or Mann Whitney U test respectively.

When both intervention groups turn out to be non-inferior to TEA regarding pain, a comparison on clinical outcome and cost-effectiveness will be done between the different intervention groups. QoR-15 is reported to have a clinically relevant difference of 8.0 points with a standard deviation of 18 points [19]. This cut-off value will be used in the analysis to determine superiority regarding quality of recovery.

10.2 Secondary study parameters

1) Pain scores during rest and mobilizing at baseline, the morning, afternoon and evening at POD 0-3 and at 2-3 weeks follow-up; will be presented as means with standard deviation or median with interquartile range depending on distribution. Comparisons will be made using the student's t-test or Mann Whitney U test

2) Proportion of postoperative pain scores of NRS ≥4 during mobilisation at POD 0-3; will be presented as percentages with 95% confidence interval (95-CI), comparisons will be made by the chi-squared test.

3) QoR-15 pre-operatively as baseline score, at POD 0, POD 3 and at 2-3 weeks follow-up; questionnaire scores (maximum 150 points) will be presented as means with standard deviation or median with interquartile range depending on distribution. Comparisons will be made using the student's t-test or Mann Whitney U test.

4) Cumulative use of systemic opioids at POD 0-3; will be presented in the measure of milligrams (mg) using means with standard deviation or median with interquartile range depending on distribution. Comparisons will be made using the student's t-test or Mann Whitney U test.

5) Postoperative complications until 2-3 weeks follow-up morbidity, according to the Clavien-Dindo classification; the number of patients divided into categories (Grade I to V) according to the Clavien-Dindo classification. These proportions will be compared between the two randomisation groups by the Chi square test, based on intention to treat.

6) Hospitalization, defined as the total number of days in hospital after surgical the surgical intervention (including readmissions within the first 30 days postoperatively); will be presented as means with standard deviation or median with interquartile range depending on distribution. Comparisons will be made using the student's t-test or Mann Whitney U test.

7) Patient satisfaction (5-point Likert scale: not at all satisfied, slightly satisfied, neutral, very satisfied and extremely satisfied); will be presented as the number of patients per category for time points t1, t2, t3 and t4 (see table 1). Comparisons between the two randomisation groups will be made using the Chi square test.

8) Time to removal of thorax drain in days; will be presented as means with standard deviation or median with interquartile range depending on distribution. Comparisons will be made using the student's t-test or Mann Whitney U test.

9) Time to removal of urinary catheter in days; will be presented as means with standard deviation or median with interquartile range depending on distribution. Comparisons will be made using the student's t-test or Mann Whitney U test.

10) Degree of mobility (on the bed, to the chair, to the toilet, outside patient's hospital room); will be presented as the number of patients per category for time points t1, t2, t3 and t4. Comparisons between the two randomisation groups will be made using the Chi square test.

10.3 Other study parameters

10.3.1 Cost-effectiveness analysis

The economic evaluation of both analgesic techniques against TEA will be performed as cost effectiveness analysis from a health care and societal perspective in this heavily affected and mostly already specialist dependent patient population. The primary outcome for cost-effectiveness analysis is the costs per total QoR score as continuous outcome measure. Additionally, we will analyse the costs per patient with adequate pain control (<35,2 % of all pain scores ≥4). The time horizon is restricted to a follow-up of 30 days after surgery. Incremental cost-effectiveness ratios are calculated, reflecting the extra costs per score of

QoR and per patient with adequate pain control. Sensitivity analyses will be performed to account for sampling variability (following bias corrected and accelerated non-parametric bootstrapping), for plausible ranges in unit costs of surgical and anaesthesiologic treatment, and for (differential) discount rates of costs and effects. Subgroup analyses will be performed for patients treated by uniportal or multiportal VATS in order to tentatively assess differences in health care efficiency. In case all analgesic strategies turn out clinically equivalent, the study will be performed as a cost-minimization analysis.

The cost analysis evaluation will include direct medical costs, out-of-pocket expenses, and indirect non-medical costs of production loss. The direct medical costs will include the costs of all analgesic procedures, therapeutic (repeat) interventions, medication, admissions, day care treatments, specialist consultations, and out-of-hospital care (like general physician, physiotherapy etc) during follow-up. With approximately over 40% of patients below 65 years of age, production losses will be estimated and based on questionnaire data concerning absence from work and lower efficiency while at work. Out-of-pocket expenses will include the costs of health-related travel, over-the-counter medication etc. Volume data will be gathered with clinical report forms, available hospital information systems, and the iMTA Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ) adjusted to the study setting (to be completed by patients at baseline T0 and 30 days after surgery T6. Micro-costing (general anaesthesia, surgical and anaesthesiologic equipment, procedure duration, involved personnel, and overhead) in participating centres will be done to estimate real unit costs. The friction costs method will be applied to derive the costs of lost productivity. After price-indexing all costs will be expressed in Euros.

The budget impact analysis (BIA) focusing on the budget of medical specialist care will be done with a planning horizon of 4 calendar years, addressing the governmental, insurer and provider perspectives. Alternative impact assessments will be made based on (i) real unit costs and (ii) reimbursements. Different national implementation scenarios of unilateral regional analgesic techniques replacing TEA will be forecasted. Budget impacts will be expressed in millions of Euros.

Since quality of life will only be adjusted during a small study period of 30 days, and only the period of acute pain (first 3 days postoperatively) is expected to have most impact on quality adjusted life years (QALY), no cost-utility analysis will be performed given the very small time frame.

10.3.2 Patient Participation (Patient preference study)

The Dutch Patient Association of Lung cancer (Longkanker NL) was consulted during the preparation of this proposal. During a personal meeting they actively participated in designing the first draft of the patient information folder and reviewing the study protocol. They are also involved in a patient preference study on preferred pain management. For this patient preference study, structured questionnaires were made in collaboration with the Dutch Patient Association of Lung cancer (Longkanker NL) and in collaboration with dr Elske van den Akker from the Medical Decision Making department at the Leiden University Medical Centre with vast experience in patient preference models.

10.4 Interim Analysis

No interim analysis is planned.

11.0 Ethical Considerations

11.1 Regulation statement

This study will be 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) and the Good Clinical Practice (GCP) guidelines.

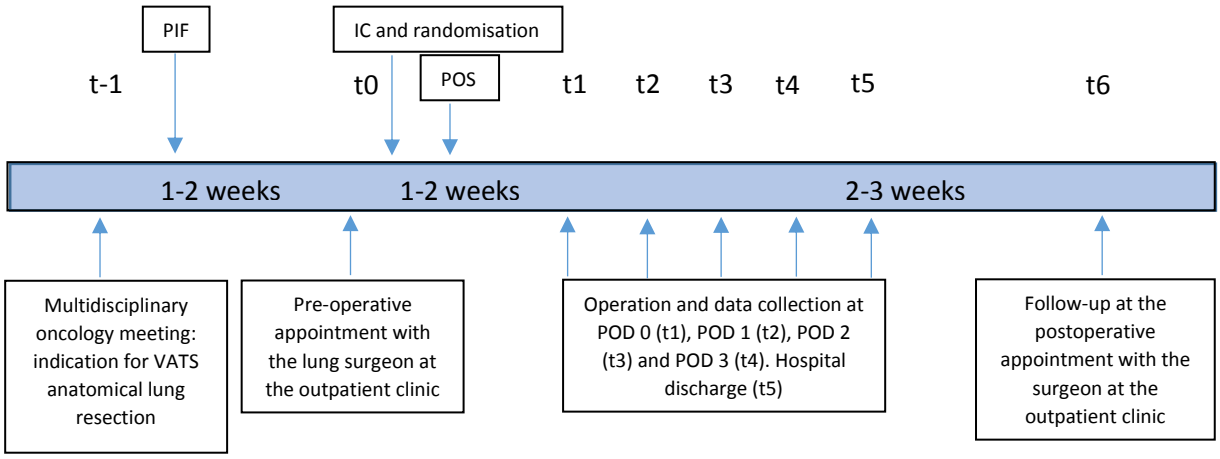
A Medical Ethical Committee with experience in medicine related studies will evaluate our project for approval. In case protocol changes are needed for approval, these will be communicated as soon as possible with the local investigators and the Dutch Trialregister. Prior to randomisation, written consent will be obtained from all the patients.

11.2 Recruitment and consent

Consecutive patients with an indication for an anatomical lung resection with the intention of performing it by VATS/RATS will be eligible (see Figure 4). This decision is mostly made during the multidisciplinary lung oncology meetings in the participating centres. From this moment, the patient will be scheduled for an appointment with the lung surgeon at the outpatient clinical. When the patient is informed about their preoperative appointment with the lung surgeon, they will also be informed about the trial by the assigned collaborator (depending on local logistics). If the patient is interested to participate in the study, the patient information folder (PIF) will be sent to their home address. Commonly, the appointment with the lung surgeon takes 2-3 weeks after the multidisciplinary oncology meetings and this gives the patient 2-3 weeks' time to read the PIF in a tranquil manner and take a well-evaluated decision as to whether participate in the study or not. When the patient attends the preoperative appointment with the lung surgeon, the lung surgeon will once again explain the study in a nutshell and the patient will have time to ask questions. If the patient voluntarily agrees to participate, a written informed consent for inclusion in this trial will be obtained by the lung surgeon, a lung surgeon in training, the (local) researcher of this study or a local nurse-practitioner, depending on local agreements. After informed consent is given, randomisation will take place by a computerised randomisation program, using Research Manager Software. Subsequently, the patient goes to the POS appointment with the anaesthesiologist to discuss the anaesthesia during the operation. At this point, patients have already been randomised and the anaesthesiologist will know the anaesthesia technique to be used during the VATS/RATS anatomical lung resection and give explanation accordingly.

Patients unable or refusing to provide informed consent will be treated according to current clinical guidelines.

Figure 4. Timeline overview of recruitment and consent



11.3 Objection by minors or incapacitated subjects

Patients younger than 18 years or patients unable to give informed consent and fill out questionnaires in Dutch will be excluded from participation in this study.

11.4 Benefits and risks assessment, group relatedness

According to a survey we conducted among lung surgeons and anaesthesiologists in the Netherlands in 2019 asking about the preferred analgesic technique used during VATS anatomic lung resection; 69% performed a TEA, 5.4% used a PVB and 18.2% used an ICNB. The variability, also confirmed through our literature review, indicates no guideline in standard care. Taking into account that TEA is the most performed technique, benefits in the patients undergoing the intervention techniques will be the omitted epidural related complications (according to our pilot study [18]): 1 day longer immobilisation, 2 days urinary bladder catheter and hypotension (reported to be present in 26% of the patients during POD 1-3).

To the best of our knowledge, the interventions used do not expose participants to additional risks compared to TEA. PVB en ICNB are not experimental and already implemented (inter)nationally. The PVB group has an equal or reduced risk of bleeding, nerve damage, insertion site infection, hypotension, post puncture spinal headache and failure of the analgesic technique compared to TEA. The ICNB group has the lowest risk of complications as it is the most peripheral analgesic technique without the insertion of a catheter. Nonetheless aforementioned risks also apply.

It is realistic to expect that patients in the intervention groups will have more episodes of NRS ≥4, therefore, we expect these patients to use more morphine to control pain.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor/coordinating investigator has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

In the setting of a multicentre trial, the sponsor ensures a patient participant insurance (by MediRisk) for all centres and each participating centre is responsible for its own liability insurance coverage.

11.6 Incentives

No incentives will be provided to study participants.

12.0 Administrative aspects, monitoring and publication

12.1 Handling and storage of data and documents

After randomisation patients will be assigned a study number and anonymous data will be registered. Data is registered and stored in Research Manager Software. Research Manager software is certified by the 'Information Security Management System 27001'. The key to the code is safeguarded by the principal investigator.

Local data management will be done by Integraal Kankercentrum Nederland (IKNL), having extensive experience with management of local data collection. Collection, storage and analysis of data will be done according to the OPtriAL data management plan.

12.2 Monitoring and Quality Assurance

12.2.1 Monitoring

Monitoring of the participating centres will be done by IKNL according to the OPtriAL monitoring plan. The sponsor location will be monitored by CTCM (Clinical Trial Centre Maastricht).

Monitoring will be done by IKNL. All centres will be visited three time during the execution of the inclusion of study participants until finalisation of the study inclusion after a minimal period of 2 years. Remote visits are planned if needed depending on inclusion rate and queries in data management. Monitoring will take place with specific attention to informed consent, data monitoring and completeness of case report form.

12.2.2 Quality Assurance Pain Techniques (intervention groups)

All participating centres will have a detailed training on how to perform a PVB and an ICNB. This training will be held by the researchers for lung surgeons and anaesthesiologists of the participating centres. For the TEA (usual care group), all participating centres should adhere to local anaesthesia guidelines. With this methodology we expect participating centres will guarantee standard execution of the interventions and high quality performance of the three different analgesic techniques.

12.3 Amendments

All substantial amendments will be notified to the accredited METC and the competent authority of the participating centres. Non-substantial amendments will not be notified tot

the accredited METC and the competent authorities, but will be record and filed by the sponsor.

12.4 Annual progress report

The sponsor/principal investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, other problems, and amendments. A list of all serious adverse events will be reported to the accredited METC every six months.

12.5 Temporary halt and (prematurely) end of study report

The principal investigator/sponsor will notify the accredited METC of the end of the study within a period of 90 days. The end of the study is defined as the patient's first visit at the surgery outpatient clinic after lung surgery. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason for such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the principal investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

Research data can be presented or published in agreement with the principal investigator only. No research data that can be traced to individual persons will be presented or published. The research data will be reported following the CONSORT guidelines.

13.0 Structured Risk Analysis

Not applicable since no new medicinal products are being investigated.

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