RESEARCH PROTOCOL

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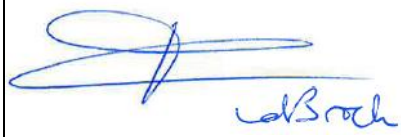
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Optimal postoperative chest tube and pain management in patients surgically treated for primary spontaneous pneumothorax; a randomized controlled trial.

Summary

Rationale: Guidelines lack high quality evidence on optimal postoperative chest tube and pain management after surgery for primary spontaneous pneumothorax (PSP). This results in great variability in postoperative care and length of hospital stay (LOS). Chest tube and pain management are prominent factors regarding enhanced recovery after thoracic surgery, and in standardised care they are crucial to improve quality of recovery and decrease LOS. We hypothesize that early chest tube removal accompanied by a single-shot paravertebral blockade (PVB) for analgesia is safe regarding pneumothorax recurrence and non-inferior regarding pain, but superior regarding LOS when compared to standard conservative treatment.

Objective: Our objective is to compare the efficacy of early chest tube removal combined with single-shot PVB versus standard treatment (chest tube for at least 3 days and thoracic epidural analgesia (TEA)) after surgery for PSP.

Study design: Multicentre four-arm randomized trial, 2x2 factorial design

Study population: Patients ≥ 16 years with PSP referred for surgery.

Intervention: 1) Early chest tube removal when the following postoperative criteria are met: no air leakage for at least 4 hours, complete lung expansion on postoperative X-ray, absence of bloody drainage. 2) Intraoperative single-shot PVB (level T2-T11) with a local anaesthetic for analgesia.

Main study parameters/endpoints: Recurrence of pneumothorax as safety measure, proportion of pain scores ≥4 on a numerical rating scale of 0-10, and LOS

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There will be negligible risks to participation since the intervention strategies are already in use in some Dutch centres and have been demonstrated feasible and safe in single centre studies. The additional burden for the participants will be the completion of questionnaires.

1. INTRODUCTION AND RATIONALE

Spontaneous pneumothorax (SP), a sudden collapse of the lung, is a clinical condition with an estimated incidence of 22.7 per 100,000 patients per year (1). This clinical condition is classified into primary spontaneous pneumothorax (PSP) when there is no underlying lung disease and secondary spontaneous pneumothorax (SSP) when underlying lung disease is present (2). Nevertheless, the occurrence of PSP is strongly etiologically associated with the presence of emphysema-like changes (ELC), blebs or bullae, which are generally identified on CT scans (3,4).

The differentiation between PSP-related changes and changes in early onset COPD is challenging. This difficulty may lead to clinical variability in diagnosing certain patient groups as having PSP or SSP. However, treatment of spontaneous pneumothorax (SP) in these uncertain cases is similar as in clear PSP cases and primarily starts with a conservative approach. Only in case of evident SSP with extensive bullous lung emphysema treatment may be different since risk of recurrence is higher in these specific cases, and hence this patient group falls out of the scope of the current study.

In case of recurrent PSP or persistent air leak (i.e. ≥ 5 days) guidelines recommend pleurodesis through video-assisted thoracoscopic surgery (VATS) (2,6). Recommendations on postoperative chest tube policy and type of analgesia are however lacking. Historically, postoperative chest tubes are put on suction and left in place for at least 3 days, irrespective of absence of air leakage. This period was deemed necessary for adequate pleurodesis and prevention of recurrence. A recent review demonstrated that different chest tube protocols were used among several studies and that LOS was directly influenced by chest tube duration (7). This study reported that chest tube removal as early as postoperative day (POD) 2 is safe. Also, Furuya showed that chest tube removal, even on the same day of surgery, is safe and feasible (8). Next to chest tube duration, one randomised trial compared suction versus water seal after video-assisted thoracoscopic surgery (VATS) in PSP (9), demonstrating water seal to result in faster chest tube removal and shorter LOS. A meta-

analysis of randomised trials further showed no advantage of chest tube suction after pulmonary surgery in general (10). However, due to lack of high quality evidence and recommendations in guidelines, great variability is induced because decisions on the chosen approach for chest tube management is mainly based on personal preferences (11). A national survey among Dutch thoracic surgeons demonstrated that 31% removed the chest tube early in case of absence of air leakage and 69% kept the chest tube in place for at least a few days ranging from 2 – 5 days (12). However, according to the guideline by the Dutch Association of Chest Physicians (NVALT), early chest tube removal is associated with less pain, more rapid mobilisation, lower risk of postoperative infection and shorter LOS (13).
In addition to the absence of high quality evidence on chest tube policy, there is also a lack of unambiguity regarding pain management after surgical treatment of PSP. Although thoracic epidural analgesia (TEA) is considered the gold standard for pain management after thoracic surgery, the use of VATS increases the interest in locoregional analgesia(14,15). The guideline on enhanced recovery after thoracic surgery (ERATS) suggests using locoregional analgesia to enhance mobilization and patient satisfaction, whereas the more recent PROSPECT guideline even recommends paravertebral blockade (PVB) as locoregional analgesic instead of TEA (15,16). The arguments are that locoregional analgesia provides sufficient analgesia without epidural related side-effects, e.g. hypotension, immobilization and urinary retention (17). In particular, PVB has shown to have a comparable analgesic effect as TEA (18,19) and plays an important role in thoracic fast-track surgery (20). Also, Xie compared PVB versus TEA versus no block in children after pleurodesis for spontaneous pneumothorax and showed that all groups had good pain control with pain scores < 4 (21). However, the earlier mentioned national survey among Dutch thoracic surgeons showed TEA to be still the most applied (78%) analgesic technique after VATS for PSP (12).
Both chest tube and pain management after surgery for PSP have been addressed by the Dutch Society of Lung Surgery (NVvL) as their knowledge gap with highest priority. The objectives of our study therefore are to compare early chest tube removal versus standard

drainage for at least 3 days, and to compare the use of TEA versus PVB in patients who undergo VATS pleurodesis for PSP. We hypothesize that early chest tube removal accompanied with a single-shot PVB is safe regarding recurrence rate and non-inferior regarding pain, but superior regarding LOS compared with the current standard treatment.

2. OBJECTIVES

Our primary objective is to compare the efficacy of early postoperative chest tube removal and single-shot PVB to usual care which comprises late chest tube removal and TEA, in patients surgically treated for PSP. Efficacy is defined as proving safety regarding recurrence and non-inferiority regarding pain, and superiority regarding LOS.

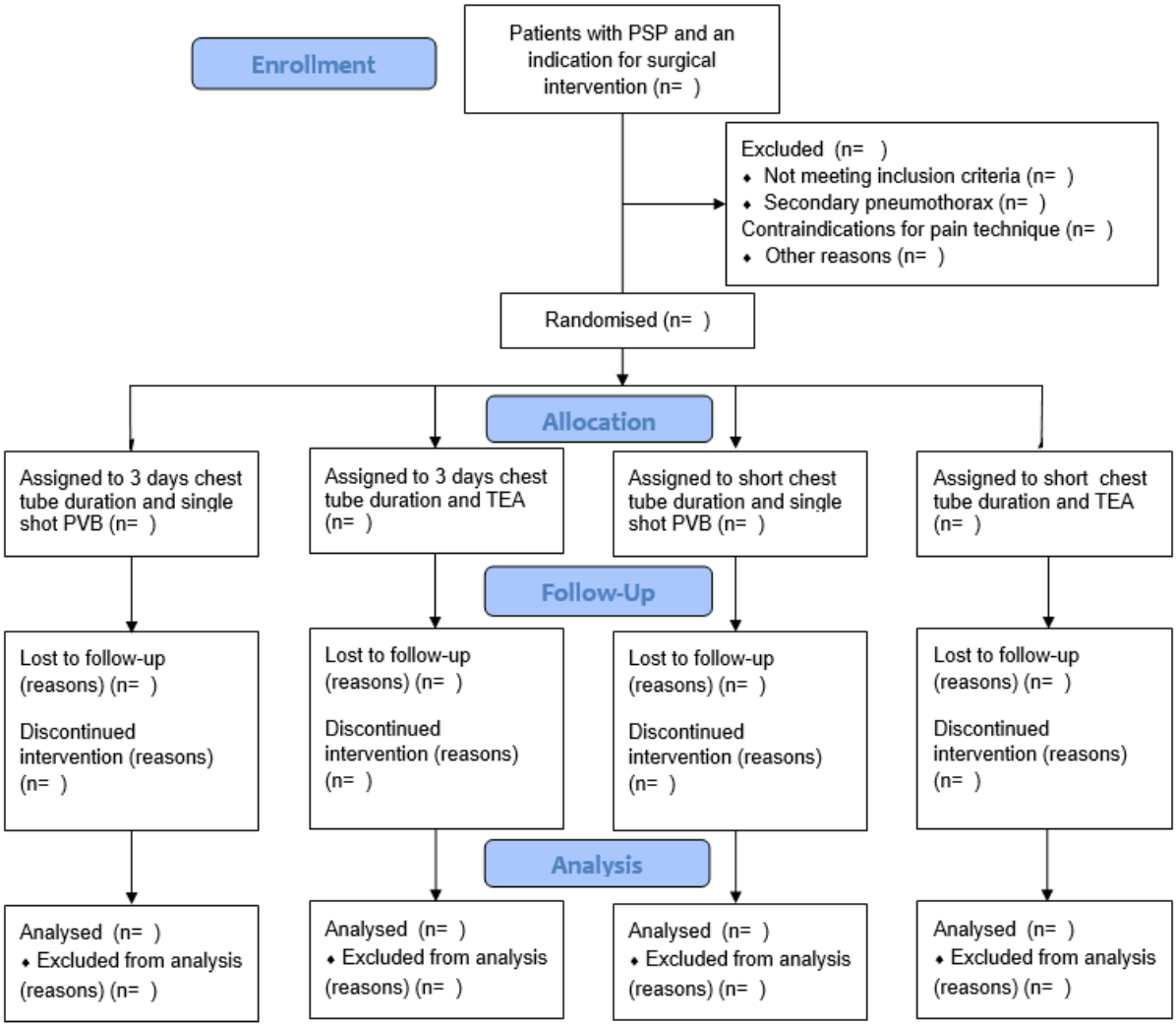
Our secondary objectives are quality of recovery (QoR), quality of life (QoL), duration of chest tube drainage, additional opioid use, postoperative morbidity, mobilization, health status, and cost-effectiveness and –utility.

3. STUDY DESIGN

A multicenter four-arm randomized trial (2x2 factorial design) comparing early postoperative chest tube removal and standard chest tube removal (after at least 3 days), as well as comparing TEA and PVB as postoperative analgesic techniques in patients with PSP undergoing VATS. This design allows independent analysis of chest tube and pain management. Early versus late chest tube removal will be compared on safety regarding recurrence and TEA will be compared with PVB on pain (non-inferiority). We hypothesize that both early chest tube removal and PVB will lead to a shorter LOS (superiority).

Since current clinical evidence does not point out which pleural intervention is superior regarding morbidity and risk of recurrence, the type of chosen surgery will be at the discretion of the hospital in which patients are being treated: either total pleurectomy or total chemical pleurodesis with talc. Randomisation will be stratified to age in which 40 years is the cut-off point and to type of centre regarding surgery (either pleurectomy or chemical pleurodesis). The CONSORT 2010 flow diagram is shown in Figure 1.

Figure 1 CONSORT 2010 Flow Diagram



3.1 Hypothesis

1. Early postoperative chest tube removal, at the earliest at 4 hours after surgery, is safe and does not lead to higher absolute recurrence rates compared to standard chest tube management.
2. Single-shot PVB is non-inferior to TEA regarding pain in patients undergoing VATS for PSP.
3. Provided that early chest tube removal is safe and single-shot PVB is non-inferior regarding pain, we expect that their combination is superior regarding LOS compared with current standard treatment, comprising late chest tube removal and TEA.

4. STUDY POPULATION

4.1 Population

All patients from 16 years who are referred for surgery for PSP are eligible for this trial. This withholds PSP patients with (contralateral) recurrence, prolonged air leak (> 5 days) at initial occurrence of PSP, an accompanied hematothorax or a profession at high risk for pneumothorax such as aviation, diving, polar explorers or working with compressed air.

As mentioned in the introduction, it is challenging to differentiate between PSP-related emphysema-like changes (ELC), blebs or bullae and changes in early onset COPD. However, as treatment in such cases is similar and distinction cannot be made based on definitions, we include inconclusive cases in our definition of PSP.

4.2 Inclusion criteria

1. All patients with a surgical indication for spontaneous pneumothorax (both clear-cut PSP and inconclusive SP)
2. Age ≥ 16 years
3. Able to read and understand the Dutch language
4. Mentally able to provide or assent to informed consent
5. Patients should preferably have a preoperative chest CT scan in order to exclude evident secondary pneumothorax. Previously made CT scans, within a time range of maximum 5 years, are accepted. The identification of blebs or bullae on CT scan is not defined as secondary pneumothorax.

4.3 Exclusion criteria

1. Previous ipsilateral thoracic surgery (except diagnostic thoracoscopy only) or ipsilateral thoracic radiotherapy
2. Underlying lung disease that provoked the pneumothorax (secondary pneumothorax): genetically proven Birt-Hogg-Dubé syndrome, periodic pneumothorax in female patients in reproductive age with known endometriosis (or known catamenial pneumothorax), pulmonary cystic fibrosis, active pneumonia, lung fibrosis, pulmonary ipsilateral malignancy.
3. Patients with extensive bullous lung emphysema detected on CT scan and
    1. treated by a pulmonologist for chronic obstructive pulmonary disease (COPD) or
    2. standard treatment (pleurodesis with bullectomy) is not possible

4. Contra-indications for TEA (infection at skin site, increased intracranial pressure, non-correctable coagulopathy, sepsis and mechanical spine obstruction)
5. Patients chronically (>3 months) using opioids will be excluded since postoperative baseline opioid requirement will be higher and TEA remains the preferred technique for these patients
6. Allergic reactions to analgesics used in the study

4.4 Sample size calculation

Chest tube management

Early chest tube removal is safe and may lead to a shorter length of stay (8), which is deemed favourable from both patients' and from health care perspective. A systematic review performed by our research group comparing early with late chest tube removal demonstrated a shorter LOS of 1.4 days in the early removal group. For the sample size regarding LOS the results of the systematic review were used. Group sizes of 164 patients with early and 164 with late chest tube removal achieve 80% power to detect a mean difference in LOS of 1.4 with a standard deviation (SD) for both groups of 4.5 and with an alpha of 0.05 using a two-sided two-sample equal variance. The difference in mean LOS of 1.4 was observed in our systematic review on early (3.9 days) and late (5.3 days) chest tube removal policies. A SD of 4.1 (with bootstrapped confidence interval based on 1000 samples (bootCI): 2.99-5.14) was derived from our retrospective study of 215 patients with a similar mean LOS of 5.0 as the mean LOS of 5.3 for late chest tube removal from our systematic review (22). Considering that type of analgesia may impact LOS and each tube removal group has equal numbers of TEA or PVB, the SD of 4.1 may be too conservative and we decided to increase the SD with 10% and used the 4.5 value instead. With a drop-out rate of 10%, 366 patients need to be included.

The shortened LOS however is only acceptable in case recurrence rates are equal between the early and late chest tube removal groups (patients' perspective). Therefore, three interim analyses will be performed under supervision of a DSMB after 90, 180 and 270 patients who completed 30-day follow-up. When the incidence of recurrences after early chest tube removal exceeds the incidence after late tube removal by more than 9 cases, then early tube removal will no longer be applied and the study will continue with the two late tube removal subgroups, unless the DSMB advises otherwise. The maximum allowable skewness of 9 extra recurrences after early tube removal is based on the following considerations. First, pneumothorax is not directly life threatening and 9 recurrences extra give a modest maximum excess of 5.49% (9/164). Second, a higher excess incidence (>=10) leads to a decrease in expected savings in LOS by well more than 20%, and undermines the economic

benefit of early tube removal too much (164 early removals save 230 hospital days and >=10 extra recurrences reduce this gain with a least 50 days).

Pain management

Regarding the hypothesis on the non-inferiority of PVB versus TEA regarding pain, no outcome data could be extracted from the systematic review. The percentage of NRS scores ≥4 during POD 0-3 is only reported in a published retrospective study from our research group, as well as verifiable from our OPtriAL study for sample size calculation (22,23). In our retrospective study the mean percentage of NRS scores ≥4 was 15.5 (bootCI: 11-20; SD: 22.4) after PVB and 20 (bootCI: 16.4-23.8; SD: 20.6) after TEA. In contrast, the OPtriAL confirmed the mean percentage of NRS scores ≥4 of 20.7 (95%-CI 16.5-24.9) for TEA, but demonstrated a higher percentage of 29.5 (95%-CI 24.6-34.4) for ss-ICNB (deemed comparable with ss-PVB), which appears more in line with clinical practice. The OPtriAL demonstrated a pooled difference in mean percentage of NRS scores ≥4 of 8.8 with a pooled SD of 26.2. Although the OPtriAL population concerned patients with lung cancer instead of pneumothorax, using these data would be more conservative and hence may lead to more credible results. Therefore, the OPtriAL data will be used as baseline assumptions to calculate our sample size for pain. Furthermore, according to a patient preference study among patients undergoing a lung resection (as part of the OPtriAL project) 87% accepted 30% extra moments of pain to have the benefits of locoregional analgesia. Therefore, an upper non-inferiority margin for the difference in percentage of NRS scores ≥4 during POD 0-3 of 25 was considered acceptable from both clinical (e.g. meaning to accept additional pain in one out of four pain measurements) and patient's perspective. Based on the Mann–Whitney U-test conservatively assuming that the actual distribution is normal and applying Dunnett's correction to control the familywise error rate (24), while comparing three independent subgroups with the same control group (TEA with late chest tube removal), we calculated that 63 patients were needed per subgroup to achieve 85% power with a one-sided significance level of 0.0089 to demonstrate non-inferiority of each treatment. With a drop-out rate of 10% 280 patients need to be included.

4.5 Feasibility of accrual

During the preparation phase of this study (between January and August 2022), thoracic surgeons from all Dutch hospitals were informed about our project. We hosted several meetings with surgeons, pulmonologists and anesthesiologists to discuss the design of this study proposal. The 28 hospitals that confirmed participation checked their annual number of surgeries for PSP, corresponding to a total number of 484 patients per year. Assuming that 10% will not meet our other eligibility criteria (e.g. coagulation disorder, allergy to analgesia),

436 patients will be eligible. Based on previous multicenter studies by our research group (MEDIASTrial and OPtriAL that had inclusion rates varying between 30-90%) we conservatively assume that at least 30% is willing to participate, corresponding to an inclusion rate of 131 patients per year. With an inclusion period of 3 years, we expect to include all required patients within the time schedule. After METC approval, local feasibility will be carried out in the participating hospitals. Prior trials have shown that local feasibility is time-consuming and arranging logistics for 28 hospitals can be challenging. Therefore, strategies will take place to initiate the first steps of local feasibility ahead of time as the process can differ per hospital. Extra personnel is budgeted to aid in this process. We do not expect all hospitals to start inclusion at the same time (starting February 2024) and we took this into account in our total inclusion rate. Further, it is important that all hospitals perform the same surgical technique. During the previous meetings, all hospitals agreed to perform either total pleurectomy or talcage. To improve uniformity in performing total pleurectomy a video of correct performance of total pleurectomy will be spread. For correct use of the Thopaz+ system, Medela, the organization which provides Thopaz+ systems, training of the personnel on interpretation of the digital chest tube drainage system. Lastly, it is crucial for the participating centers to be able to perform both analgesic techniques and an instruction course will be offered by the research group. After each hospital has started inclusions, monitoring of the study and regular meetings will be held (2 months after starting inclusions and yearly) to capture and evaluate potential inclusion or execution problems of the protocol promptly. If inclusion problems arise, a careful evaluation of the cause will take place. A newsletter will be propagated to regularly inform participating hospitals. Our study website will also contain all study information, enabling stakeholders to access information efficiently and boost feasibility. Proper information tools (folder and a video) will be made in collaboration with patients. The study website as well as the Longfonds website will propagate the study information and the information video for patients. Our patient advisory board, the patient panel and Longfonds patients have reacted enthusiastically to our research proposal. Based on our latest meetings with our patient advisory board we believe there is preparedness from patients to participate.

5. TREATMENT OF SUBJECTS

5.1 General considerations

Surgery

All included patients will undergo surgical pleurodesis through VATS, in order to achieve coalescence of the parietal and visceral pleura and prevent recurrence of pneumothorax. Pleurodesis can be achieved by either VATS pleurectomy or VATS chemical pleurodesis with talc.

With VATS pleurectomy the entire parietal pleura will be removed from approximately 2-3cm of the sympathetic trunk to approximately 1-2 cm of the mammary artery. The diaphragm will be left untreated. In case the pleura covering the region of the subclavian vessels in the thoracic outlet is adhesive, this region may be left untreated.
With VATS talcage, the entire pleural space will be sprayed with sterilized talc, using a talc dispenser until all parietal pleura is covered with talc. Mediastinal, diaphragmatic and apical pleura may be treated with talc as well.
Thus far, both mechanical and chemical pleurodesis have been shown to be effective to provide pleurodesis. Several systematic reviews on this topic were not able to demonstrate solid preferences to one technique over the other, since available literature is of low quality and with high heterogeneity (25–27). As the chosen technique depends on the local preference or doctrine within hospitals, we are able by post-hoc subgroup analysis (non-randomized, but by hospital policy) to evaluate possible differences (hypothesis generating).

If during surgery ruptured bullae are visible (generally in the apex of the lung), they will be removed with wedge resection of the lung parenchyma. In case intact bullae are present in the affected lung, wedge resection of these bullae is at the discretion of the lung surgeon. Performing a wedge resection is generally depending on the magnitude of the presence of bullae. Thus far it remains unclear whether bullectomy of intact bullae is an efficient procedure to prevent recurrent pneumothorax. Post hoc analysis of all CT images, as well as the existence of bullae during surgery, may provide further details on the question as to whether or not (and in what instances) remove intact bullae (hypothesis generating).

At the end of the operation, full expansion of the entire lung should be visualized and assured by the surgeon.

Preoperative analgesics
All patients will receive paracetamol (acetaminophen) 1000 mg. Non-steroidal anti-inflammatory drugs (NSAIDs) are prohibited in order not to intervene with the desired coalescence and fibrosis of the pleural surfaces. All preoperative analgesics administered will be registered in the case report form (CRF).

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 if necessary and additional anti-emetics based on risk factors and local protocols.

Management postoperative chest X-ray

All patients will receive a postoperative chest X-ray approximately 4 hours after surgery or ultimately the morning of POD1. In case the chest X-ray shows:

1. complete lung expansion, the chest tube can be removed if all chest tube removal criteria are fulfilled (see paragraph 5.2 Usual care for chest tube management).
2. a remaining pneumothorax with a distance of <2cm between the lung and the thoracic wall at the level of the hilum, the Thopaz+ system will be installed to a vacuum pressure of -8 cm H20 and in case of a distance >2cm to a vacuum pressure of -15 cm H20. A new chest X-ray will be made 4 hours later. If this X-ray shows:
    1. complete lung expansion and all other chest tube removal criteria are fulfilled, the chest tube can be removed.
    2. still a pneumothorax with a distance between the lung and the thoracic wall at the level of the hilum the chest tube remains in place with the same vacuum pressure. The next day the X-ray will be repeated.
3. an apical pneumothorax, the Thopaz+ system will not be adjusted since the appearance of a residual apical space is normal after apical wedge resection or bullectomy. The chest tube can be removed if all chest tube removal criteria are fulfilled.

5.2 Usual care

Two separate interventions will be investigated, one regarding postoperative chest tube management and one regarding pain management.

Usual care for chest tube management

Postoperatively, a chest tube will be left in place in order to remove redundant air and assure coalescence of the visceral pleura with the parietal part of the chest (either after talcage or pleurectomy). The thickness of the inserted chest tube will be left to in-house protocol since there is no evidence that a thicker drain is more painful (28). Common sizes are 16 – 24 French. The chest tube is connected to a Thopaz+ system (Medela inc.) and installed to a vacuum pressure of -2cm H2O. In case the participating hospital does not use the new Thopaz+ system a vacuum pressure of -5cm H20 is accepted. For usual care, the chest tube

will be left in place during a fixed period of 3 postoperative days. The chest tube will be removed at the earliest at POD 3 in case the following criteria are met:

1. The patient is lucid and capable of sitting up straight in bed on his/her own
2. No air leakage indicated by the Thopaz+ system during at least 4 hours, or <15 mL/min air leakage during at least 6 hours
3. Postoperative X ray (performed approximately 4 hours after surgery or ultimately performed the morning of POD1) demonstrating complete lung expansion at the level of the hilum.
4. Absence of bloody drainage by the Thopaz+ system

Usual care for pain management

For usual care, a TEA catheter will be placed in the awake patient after local anaesthesia of the skin. After correct placement of the epidural catheter at the 4^{th} or 5^{th} intervertebral space, a local anaesthetic (ropivacaine, levobupivacaine or bupivacaine) will be started with an additional opioid to the epidural solution according to in-house protocols. Before surgery, the skin of the incision site will be injected with a local anaesthetic. In the nursing ward, patients are allowed to mobilize under supervision when the motor function and sensibility of the extremities allows it. Placement of a urinary catheter will be left to in-house protocols, however placement will be registered in the CRF. 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 can stay in place and the epidural infusion is resumed after a bolus of 5 mL of the epidural infusion fluid. 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, a single-shot PVB is placed instead (see *intervention for pain management*). In case the epidural catheter is accidentally removed or is not placed correctly, the patient will receive systemic analgesia. This is already routine in usual care.

5.3 Intervention

Intervention for chest tube management

In the intervention groups, the chest tube will be removed at the earliest at 4 hours postoperatively in case the following criteria are met:

5. The patient is lucid and capable of sitting up straight in bed on his/her own
6. No air leakage indicated by the Thopaz+ system during at least 4 hours, or <15 mL/min air leakage during at least 6 hours
7. Postoperative X ray (performed approximately 4 hours after surgery or ultimately performed the morning of POD1) demonstrating complete lung expansion at the level of the hilum.
8. Absence of pure blood drainage by the Thopaz+ system

Safety regarding chest tube management

Despite single center studies proving the safety of early chest tube removal, no randomized data are available to compare early with late chest tube removal. Furuya specifically evaluated chest tube duration in a cohort and showed that in 85% of patients operated for PSP the chest tube could safely be removed on the same day of surgery with only 1 patient (1%) needing reinsertion of the chest tube within 1 week (8). Lacking high level of evidence studies on this topic, we performed a systematic review comparing recurrence rates between studies with early (6 studies, n=501) and late (17 studies, n=2,138) chest tube removal. The data demonstrate recurrence rates of 4.59% versus 5.57% for early and late chest tube management respectively, with acceptable heterogeneity (I^2=36% and I^2=42%). Furthermore, early chest tube removal proved also to be safe regarding complications, such as prolonged air leak and hemothorax, which were even slightly favorable after early removal. In addition, a Dutch survey among thoracic surgeons indicated that 31% of Dutch hospitals already apply early chest tube removal when air leakage is absent (12).

Intervention for pain management

Before surgery, the skin of the incision site(s) will be injected with a local anaesthetic. At the beginning of surgery, before pleurectomy, a single shot PVB will be placed at 10 levels (T2-T11) by the surgeon with a local anaesthetic and 2-3mL per site under direct thoracoscopic vision. The injection site will be chosen at the paravertebral 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 and no bladder catheter is given.

Safety regarding pain management

The PROSPECT guideline recommends to use PVB over TEA after VATS, because PVB does not have the disadvantages of TEA such as immobilization, bladder dysfunction and hypotension (16). Although this guideline refers to analgesia after VATS in general and not specifically for pleurodesis in PSP, some small studies have shown that PVB provides effective analgesia in patients undergoing VATS pleurodesis (29,30). Further, Furuya used a

single shot intercostal analgesic technique, comparable with PVB, combined with the earlier mentioned early chest tube removal which corresponded with a very short LOS, indicating sufficient pain relief by this technique (8).
Also, we evaluated all literature and found in our systematic review that locoregional analgesia is safe regarding pain, with all studies reporting mean acute pain scores < 4 (cut-off value for acceptable pain), and morbidity. In particular, Xie compared PVB vs TEA vs no block and showed that all groups had good pain control with pain scores < 4 (21). No adverse events were reported. However, due to large heterogeneity, lack of reporting on analgesia-related complications and lack of high level of evidence of included studies, firm recommendations are lacking. In our retrospective study of 215 PSP patients evaluating single-shot PVB against TEA, the proportions of pain scores ≥4 (primary outcome) were 15.5% for PVB and 20.0% for TEA (p=0.13) (22). Major complications after PVB occurred in 4% and in 10% after TEA (p=0.07) and minor complications in 5% and 13% (p=0.03) respectively, therefore providing evidence of safety. Locoregional analgesia was clearly associated with improved patient mobility and reduced LOS (1.0 day earlier discharge). In addition, our Dutch survey demonstrated that 11% of Dutch hospitals already perform a single-shot paravertebral or intercostal analgesic technique after VATS (12).

5.4 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 is insufficient, opioids 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, with the exception of NSAIDs that are not allowed. All analgesic medications and interventions given will be registered in the CRF.

5.5 Postoperative pain medication

A multimodal analgesic regime will be provided to each patient and will consist of paracetamol (acetaminophen) 4 times a day 1000 mg and oxycodone 6 times a day 5-10 mg (or another short lasting opioid) as needed. In case of insufficient pain control a long lasting opioid (oxycodone 5-10 mg) is added. If this does not result in adequate pain control additional pain medication will be administered at the discretion of the attending anaesthesiologist, with the exception of NSAIDs that are not allowed. The abovementioned regime applies only for patients in the control group if TEA is removed or when there is no

opioid in the TEA solution anymore. All analgesic medications and interventions will be registered in the CRF.

5.6 Follow up

After surgery, patients will be admitted to the ward. After chest tube removal and TEA removal (in case this is performed), patients may be discharged in case of sufficient pain control (NRS <4) with oral pain medication and sufficient self-care. In case patients fulfil the discharge criteria but remain admitted to the hospital, the reasons will be noted. During hospital stay patients will complete a digital diary for at least POD 0-3 (for pain scores, quality of recovery and EQ-5D health status). In case filling out a digital diary is not possible for the patient, a paper diary is also available. If patients with a paper diary are discharged before POD 3, they will complete their diary at home for at least POD 0-3 and return the completed diary at the outpatient clinic. After 4 weeks, patients may be seen at the outpatient clinic according to in-house protocols. All patients will be contacted by email (or by phone in case of no response) after 4 weeks in order to actualize postoperative morbidity, pain, QoR, QLQ-C30 and EQ-5D-5L. After 3 months and 1 year patients will be contacted by email (or by phone in case of no response) to actualize for ipsilateral pneumothorax recurrences, to evaluate the presence of thoracic pain with pain scores and the QLQ-C30 and EQ-5D-5L will be registered. For cost-effectiveness analyses adjusted iMTA questionnaires, the Dutch Medical Consumption Questionnaire (DMCQ) and Productivity Cost Questionnaire (PCQ), will be completed at baseline, 1 month, 3 months and 1 year after surgery.

6. INVESTIGATIONAL PRODUCT

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

As explained in the sample size section, we discussed the relevance and importance of several outcome measure with a patient panel. Although we expect the largest advantage of our interventions to be a shortened LOS with high impact on cost-effectiveness, the patient panel emphasized that short LOS is important but inferior to recurrence rate of pneumothorax. Next to recurrence rate, patients indicated acute postoperative pain to be an important topic as well. Lastly, patients emphasized uniformity in chest tube policy, the

necessity of having a bladder catheter and uniformity in radiology assessments as important factors as well. Together with the patient panel we made the following ranking: 1) recurrence rate; 2) postoperative acute pain; 3) LOS; 4) uniformity in chest tube policy; 5) the need for a urinary catheter; and 6) uniformity in radiologic assessments (CT and X-ray). In addition, the reference panel of Patiëntenfederatie Nederland advised us during the subsidy application to include QoL as outcome parameter in our study.

Primary outcomes:

1. Safety outcome: absolute number of patients with recurrence (maximum allowable difference between early and late chest tube removal groups of 9 recurrences) defined as having an ipsilateral recurrent pneumothorax after chest tube removal, confirmed by X-ray or CT within 1-year, requiring reintervention (either tube thoracostomy or reoperation) or hospital readmission.
2. The primary outcome measure (non-inferiority) for our second intervention (single-shot PVB) will be the proportion of NRS ≥4, defined as the number of NRS scores ≥4 divided by the total number of NRS measurements obtained during POD 0-3. A minimum of 11 NRS pain scores will be collected (1 at the recovery room, and 10 afterwards on the ward).
3. The primary outcome measure for our both interventions (early chest tube removal and single-shot PVB) will be LOS, defined as the total number of in-hospital days including readmissions due to complications or recurrence within 30 postoperative days. The day of surgery will be POD 0. Discharge criteria are: absence of chest tube, sufficient pain control (NRS<4) with oral pain medication, absence of fever (< 38.5 °C) and being able of self-care.

8.1.2 Secondary study parameters/endpoints

The most important secondary outcome measures will be QoR and QoL. QoR will be scored using the QoR-15 questionnaire (MCID 8) at baseline, POD 0-4 and at 4 weeks' follow-up. QoL will be measured using the EORTC QLQ-C30, which has previously shown to be of value in PSP patients when comparing VATS versus thoracotomy (31). The questionnaire will be administered at baseline and at 4 weeks, 3 months and 1 year postoperatively.

Additional secondary outcome measures:

1. Number of postoperative days having a urinary catheter
2. Postoperative morbidity during the first 30 days, defined by the Clavien Dindo classification
3. Duration of postoperative chest tube drainage

4. Postoperative pain scores at rest and during mobilization/coughing at POD 0-4 and at 4 weeks, 3 months and 1 year follow-up
5. Cumulative use of postoperative additional analgesics and opioids at POD 0-4 and opioid use at 4 weeks, 3 months and 12 months follow-up
6. Daily degree of patient mobility (scale: in bed (1), in the chair (2), to the toilet (3), outside the patient's hospital room (4)) at POD 0-4
7. Health status scored by the EQ-5D tool at baseline, POD 0-4, after 1 month, after 3 months and after 1 year follow-up
8. Patient satisfaction using the 5-point Likert scale at POD 0-4.
9. Cumulative use of additional chest X-rays and/or CT-scans (including reason)
10. Cost-effectiveness and cost-utility from a health care perspective using adjusted iMTA questionnaires, the DMCQ and PCQ, at baseline and 4 weeks, 3 months and 1 year postoperatively.
11. The impact on the national health care budget from governmental, insurer and provider perspectives. The planning horizon of the budget impact analysis will be the first 4 full calendar years following study closure.

8.1.3 Other study parameters

1. Patients' age and gender
2. Known history of pulmonary emphysema
3. Presence of pre-existent bullae on preoperative chest CT-scan
4. Thopaz data regarding the course of the amount of air leak and fluid production during postoperative drainage.
5. Performed surgical technique (e.g. chemical or mechanical pleurodesis)

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 or during initial hospital admission, inclusion and exclusion criteria are entered into a computerised database (Research Manager). If the patient is eligible, an unchangeable computer generated number will be assigned to each patient and the patient will be randomised (1:1:1:1) for one of the four groups:

1. Chest tube duration at least 3 days plus TEA (current standard/usual care)
2. Chest tube duration at least 3 days plus single-shot PVB
3. Early chest tube removal plus TEA
4. Early chest tube removal plus single-shot PVB

Randomization will be done in variable block sizes of 4 and 8.

8.2.2 Stratification

1. Randomization will be stratified for type of hospital regarding chemical or mechanical pleurodesis. All participating hospitals use the same conditional technique for pleurodesis within their hospital, although between-hospital differences may exist, since some use chemical pleurodesis with talc and others perform mechanical pleurectomy *(see 'treatment of subject' paragraph)*. As explained earlier, previous systematic reviews did not demonstrate evident differences among these techniques and firm recommendations are therefore still lacking (25–27). However, differences between these techniques may theoretically exist as a result of which we use this item as stratification factor.
2. Randomization will also be stratified by age ≥ and < 40 years, since age may influence the risk of recurrence or length of stay. Patients with PSP can grossly be subdivided into young (generally <40 years) healthy persons with PSP based on smoking induced small apical bullae, and older patients (≥40 years) with bullae based on (unknown) pre-existing emphysema. The cut-off value of 40 years is frequently used in research on our topic.

8.2.3 Blinding

Blinding regarding early or late removal of the chest tube, or regarding the use of TEA or single-shot PVB is not possible.

8.2.4 Treatment allocation

After randomisation, the patient will be scheduled for surgery with either a preoperatively placed TEA or intraoperatively placed single-shot PVB. When the patients present themselves at the preoperative screening (POS) at the department of anaesthesiology, the anaesthesiologist will have knowledge of the analgesic technique to which the patient was allocated by randomisation. 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).

At the end of surgery, a chest tube, 16 – 20 French, will be left in place through one of the VATS incisions and connected to a Thopaz+ drainage system (Medela inc.). The Thopaz+ system will be set at -2cm H2O threshold (or -5cm H20 in case an old Thopaz system is used), guaranteeing a constant negative intrathoracic pressure of -2cm H2O (or -5cm H20). Only above this level, the system will automatically apply suction until the intrathoracic pressure is assured to be below -2cm H2O (or -5cm H20). Also, after randomisation the

patients will undergo prompt chest tube removal 4 hours postoperatively when fulfilling the chest tube removal criteria or chest tube removal will be at POD3 when fulfilling the criteria.

8.3 Study procedures

Preoperatively, during the process of informed consent, patients will be asked to complete a baseline QoR-15 questionnaire, QLQ-C30, EQ-5D health status, and baseline adjusted iMTA questionnaire. A preoperative CT-scan will preferably be made to rule out possible secondary causes of pneumothorax in case a prior CT scan of the last 5 years is not available, which is standard of care.

The surgical procedures are described under paragraph 5 *'treatment of subjects'* and are part of standard general health care. In case of a pleurectomy, a total pleurectomy will be performed. In case of chemical pleurodesis, the entire pleural surface will be sprayed with talc. All procedures will be performed by VATS (either 1, 2 or 3 incisions). After surgery one postoperative chest tube will be placed mid-thoracic and a Thopaz system is used which is set at a threshold of -2cm H2O (or -5cm H20). A chest X-ray will be performed approximately 4 hours after surgery or in the morning of POD1 which is also part of routine postoperative care. In case all chest tube removal criteria are met (*see paragraph 5.2 'usual care' and 5.3 'interventions'*), the chest tube will be removed during expiration.

Regarding postoperative analgesia, the TEA catheter is placed preoperatively in awake patients and will be left in place for at least 2 days after surgery (*see paragraph 5.2 'usual care'*). Patients are allowed to mobilize under supervision when the motor function and sensibility are intact. The need for a urinary catheter will be in accordance with in house protocols of the participating hospital. In case of a single-shot PVB, patients will receive a single shot of 2-3 mL local analgesic in the paravertebral space per intercostal level from T2-T11 (*see paragraph 5.3 'interventions'*), corresponding to a total volume of 20mL. The PVB will be placed perioperatively before performing pleurectomy. No urinary catheter or mobilisation restrictions are needed with single-shot PVB. Oral painkillers will include paracetamol, oxynorm and oxycontin. NSAIDs will not be allowed.

Postoperatively, patients will be observed at the recovery room, and the first postoperative pain score will be noted. In case of hemodynamic stability and ultimately adequate pain control (NRS <4), they will afterwards be admitted to the ward. All patients will receive a diary in which pain scores (NRS 0-10; 0 = no pain, 10= worst imaginable pain) will be filled out 3 times daily (morning 2:00-12:00h, afternoon 12:01-18:00h, evening 18:01-1:59h) during 4 days. Also QoR-15 questionnaires and EQ-5D health status forms will be completed at daily basis during POD 0-3. In case patients will be discharged before POD 3, they will be asked

to complete the diary at home and return it during the first postoperative outpatient clinic appointment (in case of a paper diary).

After 4 weeks, patients may be seen at the outpatient clinic according to in-house protocols to check for complications and recurrence. In case of clinical signs of recurrence, such as chest pain and/or dyspnoea, a chest X-ray will be made to check for possible recurrent pneumothorax, which is part of routine postoperative care. All patients will provide a single pain score (NRS), QoR-15 questionnaire, QLQ-C30, EQ-5D health status, use of opioids and analgesics, and adjusted iMTA.

After 3 months and 1 year, patients will be contacted by (e)mail (or by phone in case of no response) to check for possible recurrences (possibly diagnosed at other hospitals) or clinical signs of recurrence, as well as to assess the presence of thoracic pain with pain scores (NRS) and use of opioids and analgesics. They will also receive a EQ-5D, QLQ-C30 and adjusted iMTA questionnaire to assess their health status and quality of life at these moments.

A detailed overview of all assessments is shown in the schedule of assessments (Table 1).

Table 1 Schedule of events

Assessment		Baseline/ Preoperative consultation	Day 0 surgery	POD 1	POD 2	POD 3	POD 4	4 weeks	3 and 12 months
Time point		t0	t1	t2	t3	t4	t5	t6	t7 and t8
Assessment of eligibility		X							
Written informed consent		X							
NRS pain score at rest		X						X	X
	Morning			X	X	X	X		
	Afternoon		X	X	X	X	X		
	Evening		X	X	X	X	X		
NRS pain score during movement		X						X	X
	Morning			X	X	X	X		
	Afternoon		X	X	X	X	X		
	Evening		X	X	X	X	X		
QoR-15 questionnaire		X	X	X	X	X	X	X	
EORTC QLQ-C30		X						X	X

Dosage use of opioids and analgesics		X	X	X	X	X	X	X
Patient satisfaction		X	X	X	X	X		
Recurrence PSP							X	X
Postoperative complications							X	
Patient mobility		X	X	X	X	X		
LOS							X	
EQ-5D	X	X	X	X	X	X	X	X
iMTA – iMCQ and iPCQ	X						X	X

POD: postoperative day, NRS: numerical rating score, PSP: primary spontaneous pneumothorax; LOS: length of hospital stay (including readmissions within 30 days after surgery)

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequence. In case subjects withdraw from the study after written informed consent, the reason will be asked and documented. In case no reason is given, this will be documented.

8.5 Specific criteria for withdrawal

1. In case of an allergic reaction to the investigated medicine
2. In case of secondary pneumothorax established during inclusion

8.6 Replacement of individual subjects after withdrawal

In our sample size calculation (*see paragraph 4.4)*, we assumed a drop-out rate of 10%. Therefore, we will not replace individual subjects after withdrawal.

8.7 Follow-up of subjects withdrawn from treatment

In case subjects withdraw from participation before operation, these patients will undergo treatment and follow-up according to local treatment and follow-up protocols.

8.8 Premature termination of the study

The studied interventions in this study are already used (inter)nationally. According to a survey among Dutch thoracic surgeons early tube removal may be used in 31% and late tube removal in 69%; whereas regarding pain management TEA was used in 78% and locoregional techniques in 11% (12). Therefore, we expect the interventions do not lead to unexpected events.

We also expect recurrence rate to be equal in the early and late chest tube removal group, however since our patient panel emphasized the importance of recurrence rate, a data safety monitoring board (DSMB) will be installed regarding this outcome (*see paragraph 9.5 'Data safety monitoring board'*). When the incidence of recurrences after early chest tube removal exceeds the incidence after late tube removal by more than 9 cases, then early tube removal will no longer be applied and the study will continue with the two late tube removal subgroups, unless the DSMB advises otherwise.

9. 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 investigator will take care that all subjects are kept informed.

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 which is related to the surgery or study interventions. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded according to the Clavien-Dindo classification:

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

The primary end points (both NRS scores for non-inferiority and LOS) of the study will be reached 30 days after 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

1. results in death;
2. is life threatening (at the time of the event);
3. requires hospitalisation or prolongation of existing inpatients' hospitalisation;
4. results in persistent or significant disability or incapacity;
5. is a congenital anomaly or birth defect; or
6. 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 serious adverse event.
The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs (that will be listed but not reported):

1. Regular postoperative complications after VATS pleurodesis: wound infection or dehiscence, fever, bleeding, prolonged postoperative air leakage (>5 days), pneumonia, urinary tract infection, thoracic empyema, thromboembolic events and cardiac arrhythmias.
2. Complications related to the study groups (TEA and PVB): infection at the site of injection and post-puncture spinal headache.
3. In case any of those complications occur needing readmission, we will also list them but not report them.

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 Quirine.van.Steenwijk@mmc.nl within 24 hours, using the completed report form.
The sponsor will report the 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 has first knowledge of the serious adverse events.

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 till end of the study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB)

Based on our systematic review recurrences are expected to be equal in the early and late chest tube removal. However, our patient panel emphasized that a shorter LOS (primary outcome) should not be accompanied by a higher recurrence rate in the intervention group. Therefore, a DSMB will be established to perform ongoing safety surveillance and interim analyses on the safety data. This committee is independent and has no conflict of interest with the sponsor of the study. The DSMB will monitor the safety of this study regarding

recurrence rate for early and late chest tube removal. Three interim analysis will be performed after 90, 180 and 270 patients who completed 30-day follow-up. When the incidence of recurrences after early chest tube removal exceeds the incidence after late tube removal by more than 9 cases, then early tube removal will no longer be applied and the study will continue with the two late tube removal subgroups (only randomizing and analyzing for TEA vs PVB), unless the DSMB advises otherwise. The maximum allowable skewness of 9 extra recurrences after early tube removal is based on the following considerations. First, pneumothorax is not directly life threatening and 9 recurrences extra give a modest maximum excess of 5.49% (9/164 patients in the early tube removal group). Second, a higher excess incidence (>=10) leads to a decrease in expected savings in LOS by well more than 20%, and undermines the economic benefit of early tube removal too much (164 early removals save 230 hospital days and >=10 extra recurrences reduce this gain with a least 50 days).

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

10. STATISTICAL ANALYSIS

Statistical analysis will be performed after data collection is completed. The data will be analyzed using SPSS statistical software (SPSS Inc., Chicago, IL, USA). This 2x2 factorial design will evaluate two interventions: chest tube drainage and pain management. Based on prior data, we expect additive effects of the two interventions on LOS (superiority) and we expect an interaction effect on the proportion of pain scores ≥4. Thus, results will be presented using the “at the margins” analysis as well as the “inside the table analysis”, to account for possible interactions between the treatments. The “at the margins” analysis will give estimates and 95%-CIs, comparing PSP individuals to receive an intervention with those allocated in the control group (TEA with late chest tube removal). There will be three comparisons since three interventions are investigated in the trial (32). The “inside the table analysis” is required for accurate interpretation of the effect size by presenting cell-by-cell results of the four different treatment arms for efficacy and safety analyses (33). Importantly, the data analysis will include estimates of the interaction between the treatments for independent evaluation of chest tube drainage and pain management on the outcomes (‘interaction ratio’).

10.1 Primary study parameters

The primary outcome of LOS (superiority) will be analyzed for the four study groups. LOS is defined as the total number of days in hospital after surgical intervention (including readmissions within the first 30 days postoperatively). LOS will be presented in days and presented as means with standard deviation (SD) or median with interquartile range (IQR) depending on the distribution. The primary outcome regarding pain management is the mean/median proportion of pain scores ≥4 and will be presented with 95%-CI. Comparisons will be made by student's t-test or Mann-Whitney U test, respectively. Descriptive statistics will be performed for the total sample and for all four treatment groups. These will be presented in tables with regression coefficients and 95% CI for the interaction term. This allows to interpret the magnitude of any antagonism or synergism (32). To assume superiority regarding LOS, an intention-to-treat analysis will be performed. To assume non-inferiority regarding proportion of pain scores ≥4 both an intention to treat protocol and a per protocol analysis will be performed and differences will be discussed and interpreted. Multiplicity will be adjusted for to account for a type I error. Moreover, we consider an adjustment by subgroup analysis for the influence of covariates and factors expected to have important influence on the primary outcome. The multicenter setting encourages us to pay special attention to center effects and to the role of baseline characteristics on the primary outcome. Unbalanced baseline characteristics will be determined by calculating the standardized mean differences.

10.2 Secondary study parameters

1. QoR-15 pre-operatively as baseline score, at POD0-3 and at 4 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.
2. QoL will be measured using the EORTC QLQ-C30 at baseline and at 4 weeks, 3 months and 1 year postoperatively. Questionnaire scores 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.
3. The duration of having a urinary catheter will be presented in days starting from POD 0. Results 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. Postoperative morbidity during the first 30 days according to the Clavien-Dindo classification system. Results are presented as the number of patients divided into categories (Grade I to V) according to the Clavien-Dindo classification. These

proportions will be compared between the 3 randomization groups by chi square test or Fisher's exact test, based on intention to treat.

5. Total duration of postoperative chest tube drainage 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.
6. Postoperative pain scores at rest and during mobilization during POD 0-4 and at 4 weeks, 3 months and 1 year 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.
7. Cumulative use of postoperative additional analgesics and opioids during POD 0-4 and at 4 weeks follow up 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.
8. The degree of mobility defined as an ordinal scale (in bed (1), in the chair (2), to the toilet (3), outside the patient's hospital room (4)) and will be presented as the number of patients per category for POD 0-4. Comparison between the three randomization groups will be made using the Chi square test or Fisher's exact test.
9. Health status scored by the EQ-5D tool at baseline, POD 0-3, after 4 weeks, 3 months and 1 year follow-up. Questionnaire scores 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. Patient satisfaction using the 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 POD 0-4. Comparisons between the three randomization groups will be made using the Chi square test or Fisher's exact test.
11. Cumulative use of additional chest X-rays and/or CT-scans will be documented including reasons. Evaluation of the reasons of additional use will take place using descriptive statistics. Also, the amount of additional imaging will be compared between the three randomization groups using the Chi square test or Fisher's exact test.
12. A cost effectiveness and cost-utility analysis from a health care and societal perspective of both chest tube drainage and analgesic techniques will be performed. The time horizon is 1 year, the period it takes to resolve the aftermath of a pneumothorax (and possible recurrence) in this mostly young and healthy population. Whereas safety margins regarding recurrence (interim analyses by our DSMB) as

well as upper margins for non-inferiority regarding pain are in place, we expect that the reduction in LOS and improved QoR during the POD 0-3 generate the economic benefits. Hence, cost-effectiveness and cost-utility analyses are done with total costs, out-of-hospital days during follow-up, total QoR score and QALYs. Incremental ratios are calculated for the extra costs per additional day out of hospital, per unit increase in QoR score point and per additional QALY. Sensitivity analyses are done to account for sampling variability (following bootstrapping) and plausible ranges in unit costs of surgical and anaesthesiologic treatments. Cost-effectiveness acceptability curves are drawn, showing the probability of early chest tube removal or single-shot PVB sedation being cost-effective at various levels of willingness-to-pay per QALY up to 50,000 euros. Subgroup analyses are done for patients treated by pleurectomy or chemical pleurodesis and for patients above or below under 40 years of age. Regarding cost analysis, the evaluation includes health care, patient/family, and other costs. Health care costs 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.). Out-of-pocket expenses include the costs of health-related travel, over-the-counter medication, informal help, etc. Other costs like productivity losses reflect costs of sick leave from work or lowered efficiency while at work. Data on resource use are gathered with clinical report forms, hospital information systems, and patient questionnaires. Patients complete the DMCQ and PCQ, adjusted to the study setting and extended, at POD 30, 3 months and 1 year after surgery. Micro-costing (general anesthesia, surgical and anaesthesiologic equipment, procedure duration, involved personnel, and overhead) is done in participating centers to derive real unit costs of the index interventions. The most recent Dutch manual on costing in health care or passer-by tariffs are applied to other health care resources. The friction costs method is applied to derive the costs of lost productivity. Out-of-pocket expenses are based on self-report. After price-indexing all costs will be expressed in Euros with base-year 2026.

13. With a budget impact analysis, the impact on the national health care budget will be assessed. Single shot PVB instead of epidural analgesics during surgery for PSP and supervised earlier postoperative chest tube removal will have financial consequences for the budget of medical specialist hospital care, from governmental, insurer and provider perspectives. The planning horizon of the budget impact analysis will be the first 4 full calendar years following study closure. The historical trend in yearly numbers of (adult) pneumothorax cases extracted from e.g. www.opendisdata.nl will statistically be curve-fitted conservatively to allow realistic forecasting of future yearly

case counts for the planning horizon. Linkage of the expected incidence of PSP with the trial-based differences in specialist medical care costs between the most efficient alternative treatment strategy and the standard strategy of epidural analgesics plus late chest tube removal will enable the analysis of the potential budget impact. The budget impact analysis will be incidence-based, because most treatment costs during the first year following spontaneous pneumothorax will be made within months following the actual incident. Hence, all expected costs of medical care during the first year of patients' follow-up will be attributed to the calendar year when the incident is expected to occur. National implementation scenarios will be discussed among professional societies and our involved implementation expert during the final year of the study period in order to target the most feasible (increase in) yearly diffusion rate of the most efficient alternative during the planning horizon. An alternative impact scenario will be run based on reimbursements rather than real unit costs for the projected use of hospital care. Budget impacts will be expressed in millions of Euros and the assessment will comply with the most recent ISPOR good practice guideline for budget impact analysis at the time of reporting.

10.3 Other study parameters

An additional subgroup analysis will be performed regarding age ≥ and < 40 years and between the two different surgical techniques (e.g. chemical or mechanical pleurodesis), since age and type of pleurodesis might have an influence on recurrence rate and/or LOS. Known history of pulmonary emphysema and presence of pre-existent bullae on preoperative chest CT-scan will be documented and will be checked for being a confounder for recurrence rate and/or LOS.

During the insertion of a chest tube the Thopaz+ system register the amount of air leak and fluid production per patient. After removal of the chest tube these Thopaz data will be extracted from the Thopaz+ system and the course of the amount of air leak and fluid production during postoperative drainage will be evaluated. Outcomes will be presented as means with SD or median with IQR depending on the distribution. Comparisons will be made by student's t-test or Mann-Whitney U test, respectively. Descriptive statistics will be performed for the total sample and for all four treatment groups. These will be presented in tables with regression coefficients and 95% CI for the interaction term.

Patient participation (Patient preference study)

During the preparation of this proposal our patient advisory board was consulted. During multiple meetings 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 and chest tube management. For this patient preference study, structured questionnaires were made 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

During the study period 3 interim analysis will be performed under supervision of a DSMB (*see chapter 9.5 Data Safety Monitoring Board*). The interim analysis will take place after 90, 180 and 270 patients who completed 30-day follow-up. In the intervention group (early tube removal) and the control group (late tube removal) the amount of early recurrences will be assessed. In case the intervention group exceeds the maximum allowable skewness of 9 extra recurrences, the early tube removal group will be stopped. The definition for a recurrence is an ipsilateral recurrence confirmed by X-ray or CT-scan and requires any kind of treatment.

11. 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.

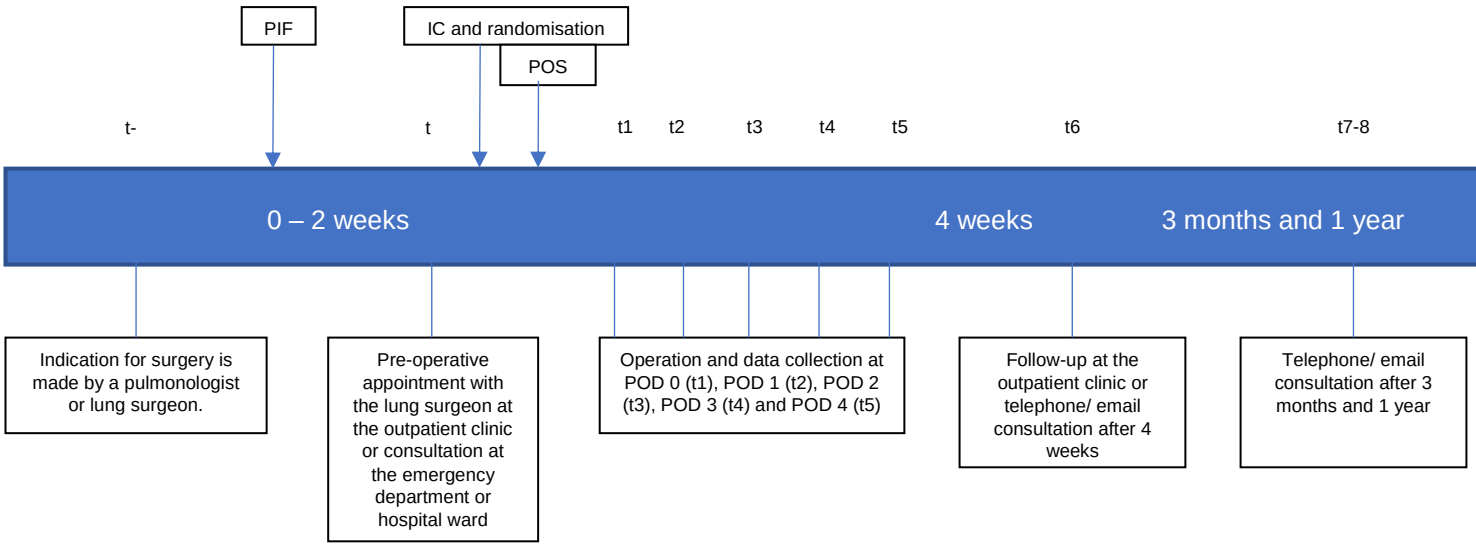
A Medical Ethical Committee with experience in medicine related studies will evaluate our project for approval. In case protocol changes are needed for approval, these will be communicated as soon as possible with the local investigators and the Dutch Trial Register. Prior to randomisation, written consent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

11.2 Recruitment and consent

Consecutive patients with an indication for surgery for (recurrent) PSP are eligible for inclusion (see Figure 2). The decision for surgery is mostly made at the outpatient clinic, at the emergency room or during hospital admittance. When the indication is made and the patient is informed, the patient will also be informed about the trial by the (principal) investigator, the (supervising) doctor (thoracic or pulmonary department depending on local logistics) or (research) nurse and will receive the patient information folder (PIF). The time between informing the patient and surgery will differ varying between 0 to 2 weeks based on the current clinical condition and urgency. However, patients will be given enough time to read the PIF and to take a well-advised decision whether to participate or not. If the patient voluntarily agrees to participate, a written informed consent for inclusion will be obtained preferably by an independent research nurse or doctor, depending on local agreements. After informed consent is given, randomisation will take place (*see paragraph 8.2.1 randomisation*). Subsequently, the patient will have a meeting with the anaesthesiologist to discuss the anaesthesia and analgesia during the operation (either TEA or single-shot PVB based on randomisation).

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

Figure 2 Timeline overview of recruitment and consent



PIF = patient information form , IC = informed consent, POS = preoperative screening, POD = postoperative day

11.3 Objection by minors or incapacitated subjects

Not applicable, since patients younger than 16 years or patients unable to give informed consent will be excluded from participation in this study.

11.4 Benefits and risks assessment, group relatedness

According to a survey among Dutch thoracic surgeons early tube removal is used in 31% and late tube removal in 69% and regarding pain management TEA was used in 78% and locoregional techniques in 11% (12). The variability, also demonstrated in our literature review, confirms the lack of a standardized guideline. However, late tube removal and TEA are mostly performed and are seen as current standard of care.

To the best of our knowledge, the interventions, early tube removal and single shot PVB, do not expose participants to additional risks compared to late tube removal and TEA. The interventions are not experimental and already implemented in some hospitals (inter)nationally. Although we expect early recurrence rate to be equal regarding early and late tube removal, we appointed a DSMB to monitor the safety on this outcome since a higher recurrence rate in the intervention group is not accepted (as indicated by our patient advisory board). Benefits of early tube removal might be shorter LOS and higher patient satisfaction. Further, single shot PVB has a reduced risk of bleeding, nerve damage, insertion site infection, post puncture spinal headache and failure of the analgesic technique compared to TEA. Benefits are omitting epidural related side-effects, such as immobilisation, urinary catheter and hypotension. It is realistic to expect that patients with single shot PVB will have more episodes of NRS ≥4 and thus needing more morphine to control the 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 also 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 ensured 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. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

After randomisation patients will be assigned a study number and pseudonymised data will be registered and stored in a computerized database (Research Manager). Research Manager software is certified by the 'Information Security Management System 27001'. The study number of a patient will be composed of a hospital specific number followed with a consecutive number (e.g. 01-001, 01-002). A subject identification code list will be used and the key is safeguarded by the principal investigator.

Local data management will be done by Clinical Trial Center Maastricht (CTCM), having extensive experience with data management according to Good Clinical Practice (GCP). All research data will be stored for 15 years. Collection, storage and analysis of data will be done according to the Pneumotrial data management plan. Furthermore, Stichting NVALT Studies will give advice on data collection and management with emphasis on FAIR principles.

12.2 Monitoring and Quality Assurance

12.2.1 Monitoring

During the conduct of this study monitoring will be assessed by NVALT datacenter according to the Pneumotrial monitoring plan. The sponsor location will be monitored by CTCM (Clinical Trial Centre Maastricht).

According to the NFU guidelines this study is of low risk, therefore one initiation visit on site and 1 remote visit will be held. If necessary one extra visit on site will be planned. Further, regular meetings will be held (2 months after starting inclusions and yearly) to capture and evaluate potential inclusion or execution problems of the protocol promptly. During the monitoring process there will be specific attention to informed consent, data monitoring and completeness of case report form.

12.2.2 Quality Assurance

Chest tube management

Through a joint educational program with the company providing the digital drainage systems (Medela inc.), personnel involved in the peri-operative care will be trained on interpretation of the digital chest tube drainage system (Thopaz+). Also, how to extract data from the Thopaz+ system will be explained. Regarding insertion and removal of the chest tube, all centres should adhere to local protocols. All participating centres should adhere to the studies chest tube removal criteria (*see paragraph 5.2 usual care and 5.3 intervention*). With this approach we expect all participating centres will properly apply the protocol regarding chest tube management.

Pain techniques

All participating centres will have a detailed training on how to perform a single shot PVB. 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 two different analgesic techniques.

Execution of pleurodesis

All participating centres performing a pleurectomy will receive a video of correct performance of total pleurectomy to improve uniformity.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All substantial amendments will be notified to the METC that gave a favourable opinion.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded 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, serious adverse events/ serious adverse reactions, other problems, and amendments.

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 8 weeks. The end of the study is defined as the last patients telephone or email consultation after 1 year of surgery for pneumothorax.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of 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 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

After trial completion, research data can only be presented or published in accordance with the principal investigator. No published or presented data shall be traceable to individual persons. Research data will be reported following the CONSORT guidelines. Published data will be findable via an open research data repository, to enable reuse in collaborative studies.

13. STRUCTURED RISK ANALYSIS

Not applicable since no new medicinal products are being investigated.

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