AKADEMISKA SJUKHUSET

UPPSALA UNIVERSITET

Effects of replacing routine chest radiography with lung ultrasound for patients undergoing thoracic surgery: A randomised controlled trial

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Abstract

Background: Patients undergoing thoracic surgery are subject to a series of chest radiographs (CXR) throughout their hospital stay. Lung ultrasound (LUS) has shown good agreement with routine chest radiograph (CXR) in several settings and feasibility in the postoperative period in observational studies.

Objectives: To assess if LUS can replace CXR in adult patients undergoing thoracic surgery in the early postoperative period.

Design: Single-centre, randomised, controlled, non-blinded trial

Inclusion and Exclusion Criteria: Inclusion criteria: Patients aged 18 years or older undergoing lung surgery (segment resections or lobectomies) providing informed consent. Exclusion criteria: pneumonectomy, surgical procedures involving pleural resections or reoperations due to complications, admittance to ICU care, pregnancy, non-available research team or if the operating surgeon or other responsible consultant deems study participation not suitable.

Intervention: LUS will be performed in the intervention group before and after chest removal. In the control group, chest radiographs will be performed routinely for lobectomies and if deemed necessary by the operating surgeon for segment resections. CXR can be performed at any time in the intervention group at the discretion of the operating surgeon or other consultant involved in patient care. Before discharge from the hospital all patients will have a CXR.

Outcomes: The primary end-point is the reduction in performed chest radiographs in the intervention group. Secondary end-points include time to chest drain removal, any adverse event leading to interventions such as reoperation or need for re-insertion of chest drain, patient satisfaction and interobserver variability of LUS.

Trial Size: Assuming a reduction of CXR in the intervention group of at least 20%, 55 patients in each group are required (two-sided alpha= 0.05 and 80% power).

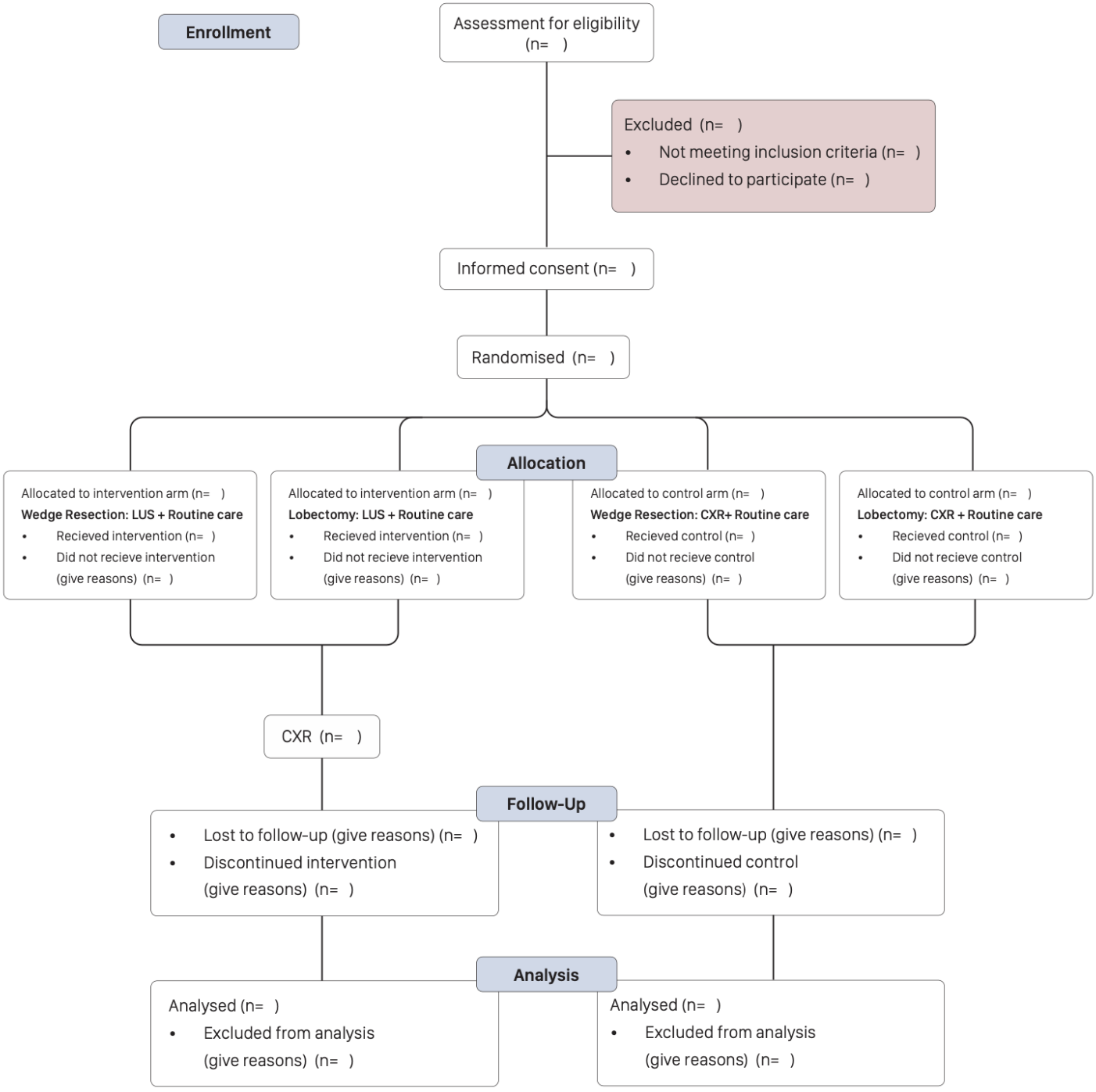
Time Schedule: Autumn 2023: Ethical and formal approval applications, education of care providers and other preparations.

Winter 2023/2024: First patient enrolled.

Spring/summer 2024: Last patient enrolled.

Summer 2024 – Autumn 2024: Data analysis and submission for publication.

Trial Flow Chart



List of Abbreviations

Abbreviation	Explanation
CFR	Case Report Form
CT	Computer Tomography
CXR	Chest Radiograph
DICOM	Digital Imaging and Communications in Medicine
EPJ	Electronic Patient Journal
GCP	Good Clinical Practice
ICU	Intensive Care Unit
LUS	Lung Ultrasound
OLV	One-Lung Ventilation
PPC	Pulmonary Post-operative Complications
sO_2	Oxygen Saturation
SaO_2	Arterial Oxygen Saturation
POD	Post-operative Day
RATS	Robot-Assisted Thoracic Surgery
VATS	Video-Assisted Thoracic Surgery

Protocol Summary

PROTOCOL IDENTITY AND OBJECTIVES

Protocol Title: Effects of replacing routine chest radiography with lung ultrasound for patients undergoing thoracic surgery: A randomised controlled trial

METHODOLOGY

Trial Design: Randomiced controlled single-centre trial

Settings: Tertiary referral hospital/university hospital

Primary endpoint: Reduction of Chest Radiographs

POPULATION OF TRIAL SUBJECTS

Description of Trial Subjects: Patients aged >18 years undergoing lung surgery

Number of Subjects: 110 patients

TRIAL TIMETABLE

First Subject In: 2024 Q1

Last Subject In: 2024 Q3

Last Subject Out: 2024

1 Introduction and Background

1.1 Patients and Peri-operative Settings

A variety of thoracic surgical procedures involve the lung and pleura such as pulmectomies, lobectomies, lobe and wedge resections and pleurodeses. These are usually performed by open thoracotomy or thoracoscopically video (VATS) or robot-assisted (RATS). In order to gain surgical access, one-lung ventilation (OLV) is often used during which the operated lung is closed off and collapsed while the non-operated lung is ventilated [1]. The operated lung is then opened and re-expanded under surgical vision and chest drain inserted before the chest is closed. After extubation the patient is transferred to the recovery unit (PACU) for observation. If air leakage and pleural effusion is negligible, the chest drain is removed. Radiographic evaluation of the lungs is performed to dismiss PPC and, patients are discharged

1.2 Current Treatment

Chest radiographic imaging (CXR) remains the standard method for detecting postoperative pulmonary complications and ensure adequate lung expansion after thoracic surgery [2]. After lung surgery, a series of CXRs can be performed depending on patient status and physician's preference. Also, the extent and method of surgery influence the number of performed CXR. A summary of CXR guidelines at our department is listed in table 1. Patients undergoing lobectomies, including segment resections, receive two or more CXR, while wedge resections receive one CXR as follow-up after chest tube removal.
The typical projection of the CXR is antero-posterior with the patient either semi-recumbent or standing up [3]. Lateral projections are performed if requested.

	PACU	Clamped chest tube	Post-removal of chest tube
Lobectomy			
Segmental lobectomy			
Bilobectomy			
Wedge resection			

Table 1: Suggestion of CXR distribution in routine lung surgery, by surgical method. PACU: Post-Anesthesia Recovery Unit.

1.3 Trial Interventions

For detailed description of interventions, see section 8.

Lung ultrasound (LUS) is a well-established, non-invasive method that has shown good agreement with CXR. The method has several advantages, such as the omittance of radiation, being cost and time effective and allowing the patient to be examined in his or her own bed. Although multiple protocols exist in many different settings [2], LUS regarding lung aeration and PPC's have yet to be refined in patients undergoing lung surgery. Observational studies have shown that LUS performs comparable to, or even superior to CXR [4, 5, 6], yet randomized controlled studies are lacking. A more comprehensive description of data collection will be presented in section 8.2.

Lung Ultrasound

Lung ultrasound is a non-invasive method of investigating pulmonary pathology. As ultrasound cannot directly visualize gas, the sonographer instead must rely on specific signatures of artifacts that develop as pathology progresses. As the vast majority of pulmonary pathologies, >95%, reach the visceral pleura, they can therefore be subjected to semiotic interpretation [7, 8]. When extravascular fluid accumulates in the lung parenchyma, or when air is distributed in between the pleural membranes, these signature patterns appear, allowing semi-quantification and qualitative assessment of both lung aeration and the occurrence of air leaks. Lung ultrasound is widely used in clinical practice and has in several studies been proven equal to, or more sensitive and specific than comparable methods of investigation such as CXR [6].

Lung aeration score

As LUS provides real-time information of pulmonary disease, it has been used to sequentially screen patients. Global assessment of the lungs has been strongly associated with tissue density and aeration. Commonly a scoring system based on loss of aeration in protocolized points or regions of the lung is used. Although the number of regions assessed may differ, scoring is based on the number and appearance of artifacts, where a reduction of artifacts indicates recovery from pathology [9]. A general cut-off score has not yet been defined, however a score > 47% of possible maximum score is indicative of poorer outcome and associated with more various pathologies [10]. In an observational study comparing global

scores to those omitting posterior scores, the authors did not find any significant difference in diagnostic accuracy when scanning only anterolateral regions of the lungs [11].

Pneumothorax

As air infiltrates the space between the visceral and parietal pleura it produces a physical barrier for the propagating ultrasound beam. Contact with the visceral membrane during breathing is abolished and the sonographic image produced is characterized by a visual absence of pleural sliding and reverberating of the parietal pleura. Ergo, no signature of artifacts can be produced deeper than this. Although this sign is not exclusive to pneumothorax it warrants further assessment. A pneumothorax is usually limited and borders a region of the lung not affected by the air leak. At this border the sonographer can identify the transition from abolished lung sliding and present, a lung point, highly specific to pneumothorax [7, 11].

Estimation of the size of a pneumothorax is possible with LUS. As gas accumulates in the least dependent areas of the pleura, this has implications for estimation of size. Supine patients will display an accumulation of air anteriorly and in a slightly caudal direction. As the pneumothorax increase in size, the lung point will move more laterally. In very large pneumothoraces, the entire anterior and partially lateral surface will be affected, also making detection of a lung point [8, 11]. Thus, any change from supine to erect position of the patient will shift the distribution of gas in the pleural cavity. A pneumothorax is considered small if the distance between the location of a lung point and chest wall is less than 2 cm, and large if greater than 2 cm [12], however the depth of eventual lung collapse cannot be evaluated. When compared to CT scan of lung collapse, a lung point anterior to the mid-axillary line indicated a collapse of $\leq$ 10 %; on the mid-axillary line as 11–30 %, and posterior to this line >30 % collapse [13].

Pleural effusion

The presence of pleural effusion can be accurately identified and reliably quantified using LUS. Fluid in the interpleural space creates a hypoechoic image confined between the diaphragm and either aerated or more commonly by the superimposed pressure collapsed lung parenchyma [9]. Detection of pleural effusion by ultrasound has a 93% sensitivity [7, 8, 14, 15] and can identify as little as 5 mL. Volume can be estimated through the measured

dimensions of the ultrasound image inserted in a simple formula. This estimated value has been shown to has good level of accuracy when compared to aspirated actual volume [16].

Patient Satisfaction

If in any case patients are subjected to cross-over from the investigational arms of the study to the control arms with routine care with CXR, a sub-group analysis will be conducted. This analysis will rely on a semi-quantitative questionnaire designed to encompass the dimension of patient satisfaction between the two methods of examination.

1.4 Adverse Effects of LUS

Adverse effects of LUS are very few and considered to be minuscule. Long term exposure of medically indicated ultrasound can in specific instances produce tissue damage in relation to thermal and mechanical energy dissipation from the probe [18]. This risk is mitigated partly by the brief examination period, and partly from the use of relatively low frequency transducer and mechanical index, or output (MI). MI represents the non-thermal biological effects, mainly cavitation, and is recommended ≤ 0.4 to account for the difference between the surface MI displayed on the ultrasound machine and in situ MI in exposed tissue. Thus, increasing MI should only be made in imaging requirements, to a maximum threshold of 1.9 [19]. Furthermore, due to varying body composition in patients, an individual level of pressure from the probe may be applied to the patient to optimize imaging. This could lead to minor, transient pain in more sensitive subjects, especially in examination points adjacent to the operation site.

As with all point-of-care examinations there is a small, but not negligible risk of transmission of microorganisms from the transducer. This risk is mitigated through the application of routine hygiene and disinfection of the machine and instruments.

1.5 Risk and Benefits

Assessment with lung ultrasound is well-established and regarded as a safe and non-invasive method of examination of thousands of patients every day.

1.6 Ethical Justification and Trial Rationale

Evidence suggests that LUS is a valid alternative to radiographic standards such as CXR and Computer Tomography (CT) for a large variety of patients. LUS is also recommended in international guidelines [19].

Patients will be enrolled for study participation only with informed consent and will have the ability to withdraw their consent at any time they choose. The consenting patient will be provided written and oral information about the trial at a time parallel to an information meeting with a nurse and physician at the pre- and post-operative ward.

All patient care in the trail will receive routine care apart from the method of examination. Post-operative routine care is based on compiled evidence and encompasses both clinical and diagnostic dimensions. Thus, patients in the control group will not be exposed to any additional risks.

This study's main investigator is a critical care specialist nurse experienced in sonography. The investigator reports all findings from the LUS examinations to the treating physician, or surgeon, who may at any point during this study requests a CXR study if the patient's wellbeing is considered to be jeopardized, thus leading to crossover to control group and routine care with CXR.

No biological material will be collected in this trial, thus no bio-bank will be formed.

1.6.1 Ethical Conduct of the Trial

This trial will be approved by the Regional Ethics Committee in Uppsala. The trial will adhere to the trial protocol, GCP and the Helsinki Declaration (Seventh Revision). If any part of the protocol needs to be amended, changes shall be compliant with the Ethics Committee. For public transparency the study will be registered on the online database https://clinicaltrials.gov.

1.6.2 Disclosure of Investigator Relationship

The principal investigators of this study are a critical care specialist nurse (S. U.) and an anesthetist-intensivist physician (J. J.), employed by the same clinic. The latter is a doctoral supervisor to the former. J. J. is to supervise the process of the study and will act as the secondary observer of the LUS examinations. The main doctoral supervisor (J. H-J.) and doctoral supervisor (J. E.) are co-authors of the study.

1.6.3 Outcome Considerations

A reduction in the number of performed CXR has been suggested in several prospective observational studies [2, 17, 21, 22]. It has also been inferred LUS has superiority in both sensitivity and specificity in certain aspects of lung diagnostics. Its favorable lack of ionized radiation makes it in the public's interest to research the methods' possible impact on patients who are routinely examined with CXR.

Although a large body of research has been made on LUS over the last decade, there are still challenges in establishing consensus in specific outcomes. Guidelines and expert statements however now exist to navigate future research based on evidence and will be applied to this trial [19]. To the knowledge of the investigators of this trial, no prior randomised research has been conducted to elucidate the relationship between adult lung surgery and LUS.

The rationale for choice of outcomes in this study is:

1. A LUS composite of outcomes routinely monitored with CXR could possibly benefit patients.
2. A protocol based on 8 regions of interest should suffice, as opposed to basing a global score on more regions. In emergency settings, a protocol based on 6 regions is usually applied [8], while other studies have included up to 28 regions. Most of studies with higher numbers of examined regions include posterior regions and further sectioning of the thorax. Although evidence suggest that adding a posterior score contribute to higher global scores in specific pathology, it generally seems to have a lower diagnostic accuracy [8, 10].
3. The concept of limiting the number of scanned regions is based on mainly two factors in this trial. (1) The number of regions scanned in this trial are higher than those in emergency settings because of the inhomogeneity of surgical site, however no posterior surgery is performed, thereby omitting posterior scanning. (2) Scanning of an affected region refers to a point withing the specified anatomical region on the chest. Most disorders, however, have substantial extension and apart from certain signs, such as lung point in pneumothorax, an artifactual sign will also be visible adjacent to the probe position [8]. Another rationale is that combining the aeration score with the search of a lung point will lead to more extensive scans.

1.7 Trial Conduct

This trial will be conducted according to the Helsinki Declaration in its latest revision. The project will be registered on to www.clinicaltrials.gov ahead of the start of the trial. No major deviations from or altering of the protocol will be made without further review and approval of the ethics committee and authorities. Enrollment to the trial will commence after the approval from same instances. Upon trial conclusion a manuscript with the main points of the protocol, including description of design, rationale and analysis plan will be submitted to a journal in English language.

2 Trial Objectives

2.1 Primary Objective

Evaluation LUS as the primary method of examination of aeration and PPC's during the post-operative period.

2.2 Secondary Objectives

- Correlation of early, or delayed removal of chest tubes, with LUS as the primary method of evaluation of pneumothorax.
- Inter-observer agreement between critical care nurse specialist and anesthesiologist.
- Evaluation of patient satisfaction.

3 Trial Design

3.1 Trial Design

An investigator-initiated, single-centre, parallel-group trial of LUS versus CXR in patients undergoing lung surgery.

3.2 Randomisation

1:1 randomisation will be performed through web-based randomization according to a computer-generated allocation sequence list. Allocation will be made to an investigational group, and control group, respectively. Each group will allocate in two arms depending on surgical method described in section 5. Each patient will be allocated with a unique screening-number.

3.3 Blinding

The principial investigator performing the LUS will not, by self-evident reasons, be blinded to the randomization. The fellow researcher (J. J.) during follow-up analysis of collected images will be blinded to the patients' surgery and the original LUS examination results.

Blinding of type and circumstance of the surgery will also be applied in the subgroup analysis of patients who are subjected to crossover from investigational arm to control.

3.4 Participant Timeline

The aim is to enroll patients as soon as they are identified to fulfill the inclusion criteria. Selected subjects will be given written and verbal information parallel to admission to the surgical ward by the scientist responsible for the study. Only patients who have given written informed consent are to be included in the study. Allocation to either LUS or CXR upon admittance to the pre-operative ward and will continue the allocated intervention until formal discharge by the treating physician.

Pre-operative Events:

Will take place in the surgical ward reception as part of admittance.

- Trial information
- Informed consent

Peri-operative Events: Will take place in the post-operative recovery ward.

- Lung Ultrasound or CXR
- Physiological and Ventilatory parameters

Post-operative Events: Will take place in the surgical ward.

- Lung Ultrasound or CXR
- Physiological parameters
- Comparative CXR in the investigational group
- Data collection from radiography records
- Data collection from medical records
- Inter-observer agreement study of collected LUS images
- Sub-group analysis of Patient Satisfaction for patients subjected to cross-over, i.e., receiving both LUS and CXR.

4 Selection of Participants

4.1 Inclusion Criteria

- Patients aged ≥18 years
- Segmental, partial or wedge resection lung surgery, or lobectomy
- Written informed consent
- Available research team for measurements

4.2 Exclusion Criteria

- Pregnancy
- Re-surgery due to complications related to the original surgery
- Need for critical care **OR** admittance to the ICU
- Patient withdrawal from the study

4.3 Participant Discontinuation and Withdrawal

4.3.1 Discontinuation and Withdrawal at the Choice of the Participant

Subjects may at any time request to be discontinued from the study. This process will follow the national regulations in Sweden.

Discontinuation and Withdrawal at the Choice of the Investigator

The principal investigator may at any time withdraw a subject from the study if it is deemed to be in the patient's best interest.

Discontinuation and Withdrawal at the Choice of the Treating Physician

This trials' main investigator is a critical care specialist nurse experienced in sonography. The investigator reports all findings from the LUS examinations to the treating physician, or surgeon, who may at any point during this study requests a CXR study if the patients' wellbeing is considered to be jeopardized, thus leading to crossover and exclusion of the subject from the study. To minimize accidental group crossover due to misinterpreted LUS findings, an educational effort in methodology will be implemented prior to commencing of the trial.

5 Trial Interventions

5.1 Experimental Intervention

All patients randomized to the investigational group will receive Lung ultrasound (LUS) with the use of transducers of varying frequency output (5– 10 MHz) on a Philips EPIQ 7 ultrasound machine. Examination will be performed by the principial investigator during the patients' hospital stay. Since routine care with CXR differs based on the extent of surgery, allocation will be made in two interventional arms. The timing of examination and data collection is summarized in section 8.2.

5.1.1 Lobectomy Intervention Arm

Patients undergoing multiple or segmental lobectomy will receive two examinations with LUS in the investigational group.

5.1.2 Wedge Resection Intervention Arm

Patients undergoing multiple or single wedge resection will receive one examination with LUS in the investigational group.

5.2 Control Intervention

Patients randomized to the control group will receive routine care with CXR. The definition of routine care is defined by the number of CXR examinations in the setting of optimal post-operative care for the thoracic surgery population at the centre where this study is conducted. A consensus of the number of examinations with CXR was reached within the pulmonary surgical team and approved by the senior surgeon. Thus, as with the investigational group, the control group will be allocated into two arms Depending on the method of surgery.

5.1.1 Lobectomy Control Arm

Patients undergoing multiple or segmental lobectomy will receive two examinations with LUS in the investigational group.

5.1.2 Wedge Resection Control Arm

Patients undergoing multiple or single wedge resection will receive one examination with LUS in the investigational group.

5.3 Co-intervention

All patients in the investigational arm will receive a CXR before discharge. The examination will be ordered in conjuncture with decision of patient discharge from the hospital by the treating or attending physician.

6 Outcomes

6.1 Primary Outcome

The primary outcome is a reduction in CXR in patients undergoing thoracic surgery when LUS is the primary method of investigation for PPC.

6.2 Secondary Outcomes

6.2.1 PPC-driven Interventions

a. **Variable Name:** Re-insertion of Chest Tube
   Variable Description: The need for re-insertion of chest tube because of clinical deterioration, and/or verified clinically relevant PPC.

b. **Variable Name:** Delayed removal of Chest Tube
   Variable Description: Number of patients in need of prolonged care with Chest Tube.

c. **Variable Name:** Time to Chest Tube removal
   Variable Description: Time, in hours, to eventual removal of Chest Tube.

6.2.2 Adverse Events

a. **Variable Name:** Missed Care
Variable Description: The number of missed diagnoses of PPC based on results from CXR in patients subjected to crossover.

6.2.3 Psychometric Outcome

a. **Variable Name:** Patient Satisfaction
Variable Description: Sub-group analysis of the patient experience and satisfaction for patients receiving both LUS and CXR, measured through quantitative psychometric questionnaire.

6.2.4 Inter-rater Variability Outcome

a. **Variable Name:** Inter-rater Variability
Variable Description: Post-hoc comparison (JJ) of ultrasound images collected by primary investigator (SU). Evaluation of images are recorded in separate CRF.

7 Safety

7.1 Definitions

Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant included in this study, even if it does not have any relationship with the examination itself. An AE can be any unfavorable or unintended sign or abnormal finding or symptom. It is also

regarded as an AE if patient data management is comprised resulting in breach of privacy, integrity, or implication of any participant in this study.

Adverse Reaction

An Adverse Reaction (AR) is defined as any noxious and unintended medical response to the examination during a clinical trial. A potential AR can be topical reaction to ultrasound gel.

7.1.1 Assessment of Adverse Events

7.1.1.1 Assessment of Intensity

Each AE is to be classified by the investigator as mild, moderate, or severe.

Mild: Acceptable. The subject is aware of the symptoms or signs which are tolerable.

Moderate: Disturbing. The AE is discomfort enough to interfere with usual daily activity.

Severe: Unacceptable. The subject is incapacity to work or to do usual daily activities.

7.1.1.2. Assessment of Causality

Unlikely: The event is most likely related to an etiology other than the investigation.

Possible: A causal relationship is conceivable and cannot be dismissed.

Probable: Good reason and sufficient documentation to assume a causal relationship.

7.1.2 Serious Adverse Events

Each AE will be classified by the investigator as either serious or non-serious. Seriousness is not defined in medical terms, but a result or an outcome. An AE is defined as a Serious Adverse Event (SAE) if it:

- results in death
- is life-threatening
- requires prolongation of inpatient hospitalization
- results in persistent or significant disability or incapacity
- other reason by the investigator deemed serious

7.2 Reporting

All AEs will be recorded on a separate and designated form in the CRF.

7.2.1 Reporting of Serious Adverse Reactions and Events

In addition to the above mentioned, any SAE will also be reported by the investigator to the treating physician immediately, and to the sponsor on a separate SAE form withing 24 hours after the SAE has been communicated to the investigator. Follow-up information describing the outcome of the SAE and action taken will be reported as soon as it is available. The original SAE form must be filed with the CRF.

7.3 Risks and Issues in the Current Trial

LUS is a well-established method of examination in clinical use.

8 Procedures, Assessments and Data Collection

8.1 Inclusion Procedure

8.1.1 Screening

All patients planned for thoracic lung surgery will be screened for eligibility of enrollment. The principal investigator will screen the surgical planner for candidates.

8.1.2 Procedures for Informed Consent

Patients eligible for trial enrollment will be given oral and written consent by the principial investigator as a part of the patient registration prior to pre-operative admittance to the surgical ward. The information will be given in a separate room and will be in compliance with applicable regulations. The potential participant will be offered time for consideration up until pre-operative admittance to the surgical ward, should the patient choose. Otherwise, informed consent will be collected as soon as possible.

8.2 Data Collection

8.2.1 Method

Radiographical data and data concerning vital parameters and ventilatory settings will be obtained from electric patient journal (EPJ). Data are recorded from various sources, apart from patients' medical records and connected applications related to managing diagnostic data, e.g., radiographic or lab results. Clinical Report Forms (CRF) will be scanned and converted to digital copies for formatting.

8.2.1.1 Lung Ultrasound Case Report Form

All collection of data during the LUS examination will be collected in a specific Clinical Report Form (CRF). The LUS-CRF (Appendix 1) consists of six domains: Aeration Score, Pneumothorax, Pleural effusion, Atelectasis, Subcutaneous emphysema, and Physiological parameters. Collection will be made on a Philips EPIQ ultrasound machine using three different probes: Linear transducer L12-3 (3–12 MHz, focal depth at pleural line, maximum depth at 12 cm); Phased array transducer X5-1 (1–5 MHz, focal depth at costophrenic sulcus, maximum depth at 20 cm); and Abdominal transducer C5-1 (1–5 MHz, focal depth at costophrenic sulcus, maximum depth at 20 cm). Mechanical index will range from 0,4–1,2.

Aeration Score

Semi-quantitative sonographic signature pattern of artifacts indicating loss of aeration in lung parenchyma, i.e., inadequate lung expansion. Ranging from 0–12 scoring points, visualized in two anterior and lateral regions, respectively, in each hemithorax, accumulated to a global score [20]. Since the pleural interface is investigated, the linear probe (L12-3) will be used.

Artifacts indicative of aeration loss are based on subpleural interaction of ultrasound beam, air and fluid accumulation in interlobular septa. This intermingling of air and water creates vertical comet-like artifacts (B-lines) indicative of interstitial syndrome and non-aerated lung. Aeration loss is scored by both quantitative and qualitative assessment of B-line number and the distance between each separated B-line, in four regions of respective hemithorax. Score 0 is defined as the absence in a scanned region. Score 1 is defined as $\leq$ 3 well-separated B-

lines; Score 2 as >3 coalescing B-lines; and Score 3 is ultimately defined as any subpleural consolidation [8, 19, 20].

Pneumothorax

Using the linear probe (L12-3), a longitudinal scan for correct intercostal placement of probe will be made followed by transverse scan of the pleural interface. Patterns indicating pneumothorax based on artifacts (abolished lung sliding, lung point, etc.) will be searched after in above-mentioned regions. Since the first, but not sole pathognomic sign of pneumothorax is abolished lung sliding, an algorithm is implemented to effectively exclude pneumothorax and to reach high sensitivity and specificity in correct diagnosis [7]. Pneumothorax is thus only confirmed when the transition between abolished normal lung sliding can be found, the so-called lung point. Failure to find a lung point when other signs indicate a pneumothorax will be recorded and reported as possible, yet unconfirmed. The lung point is representative for the extension and beginning of the pneumothorax in the current postural position (semi-recumbent, 30°). A visualized lung point will be recorded by anatomical reference lines such as the parasternal, mid-clavicular, anterior, mid-, and posterior-axillary lines [13].

Pleural Effusion

Visualization of eventual pleural fluid will be made in the latero-inferior region cephalad to the diaphragm in semi-recumbent, 30° position, using the phased array or abdominal transducer (X5-1; C5-1). Estimation of volume will be measured with the ultrasound machine digital calipers in centimeters from chest wall, and from diaphragm to collapsed lung, respectively. The product of these two measurements and a factor of 70 will be used to estimate the effusion volume in milliliters [8].

Atelectasis

A consolidation is on LUS is visualized as a tissue-like structure within the lung itself. Differentiating this structure from other types of consolidation (i.e., pneumonia or tumor) is done by qualitatively examining trapped air within partially collapsed larger bronchioles within the consolidation. These pockets of gas are in the case of atelectasis fixed in position throughout the respiratory cycle. Also called static air bronchograms are thus trapped air

resulting from primarily resorption atelectasis [23, 24]. The choice of transducer will depend on which region is scanned.

Subcutaneous Emphysema

The presence of subcutaneous emphysema (SCE) will be diagnosed based on artifacts distributed superficially to the pleural interface detected by any transducer, thus hindering adequate propagation of the ultrasound beam [7].

Physiological Endpoints

Vital parameters will be collected parallel to each examination, LUS and CXR respectively. These parameters include transcutaneous oxygen saturation and heart rate, respiratory rate, blood pressure (non-invasive and invasive when available), and oxygen demand described as administrated supplemental oxygen.

8.2.1.2 Ventilatory Endpoints

Ventilatory settings will be collected from the EPJ retrospective to surgery and will include ventilatory mode, tidal volume and minute ventilation, and peak or plateau pressure.

8.2.1.3 Patient Satisfaction Endpoint

Patients in the subgroup consisting of patients subjected to group cross-over will be handed semi-quantitative questionnaires before discharge from the hospital. This questionnaire will with a 15-item Likert-type design encompass psychometric dimensions regarding patients' experiences and satisfaction with both LUS and CXR examinations. Surveyed dimensions will focus on patients' attitudes toward LUS and CXR, and their perceptions of interaction with the clinicians performing the examinations. Patients will also be asked to assess the provision of care by considering various aspects of the examination process, patient expectations, given and understanding of information, and opinion on being examined by a specialist nurse rather than a physician.

The possible answers in the questionnaire range from sets of satisfactory to non-satisfactory statements; Very satisfied, satisfied, neither, un-satisfied, and very un-satisfied. A second set of answers range from low to high agreement to the posed statement; strongly disagree,

disagree, neither, agree, and strongly agree. A summated rating score will then be collected from each responder. A higher score is by design indicative of a more positive attitude toward the question being asked. To achieve this, a reverse direction of optional answers will be applied when questions are negatively worded.

8.2.1.4 Chest Radiograph

Data from CXR in the control group will be collected when all examinations have been made to a participant. Radiographic data will be collected from the hospital digital service for radiographic diagnostics along with written interpretation of the images. Clinical diagnosis will be based on radiologist and surgeon interpretation.

CXR Endpoints

- Patient positioning
- Qualitative description of aeration
- Pneumothorax (yes/no)
    - Estimated size in centimeters
    - Location
- Pleural effusion (yes/no)
    - Location
    - Estimated size in centimeters
- Atelectasis
    - Location
- Subcutaneous emphysema
    - Location
    - Extension

8.2.1.4 Inter-observer Agreement

Appearance of LUS-artifacts are operator-dependent and therefore a degree of inter-observer variability could be expected. Therefore, a secondary evaluation and interpretation of collected LUS images will be made by a second investigator (J. J.) who is blinded to the

primary investigators results. A statistical analysis will then be made on the inter-observer agreement in LUS endpoints.

8.3 Timing

Appendix 4 shows and overview of the timing and variables defined in this section.

Pre-operative (screening procedure)

Subjects will be identified through the operation planning list and assessed for study eligibility.

- Patient information about the study
  Collection of informed consent
- Randomisation

Baseline variables (not collected in the screening procedure)

- Gender
- Age at randomization (date of birth)
- Date of admission to hospital
- Prior lung resection surgery (y/n)
- Co-morbidities

Post-Anesthesia Recovery Unit (PACU)

The following will be collected for patients in the lobectomy investigational and control arms.

- LUS or CXR
- Physiological parameters
- Present air leakage in chest tube (y/n)
- Volume of air leakage

Post-operative Surgical Ward

- LUS or CXR
- Follow-up CXR for patients in the investigational g

9 Data Handling and Record Keeping

9.1 Data Management

All individual patient data collected from LUS examination will be recorded in the CRF and may be digitalized for formatting. The output files from electronic monitoring software will be exported individually to excel files. All files shall be collected and formatted for further analysis using appropriate software. Digital images and data collected from LUS examinations will be stored in hospital servers for digital image storage and management, accessible through a dedicated application (DICOM). Statistical analysis will be made by a statistician.

9.2 Confidentiality and Access to Data

All original records, including informed consent, CRFs and relevant correspondence will be archived and coded for animosity at the trial site for 10 years. Database files and code access key will be accessible only to researcher connected to this trial and authorities upon request.

10 Statistical Analysis

10.1 Sample Size Estimation and Power Calculations

10.1.1 Sample Size Estimation of the Primary Outcome

The amount of lung surgery fitting the inclusion and exclusion criteria for this study is currently estimated as: 110 lobectomies, including segmental; 100 wedge resections, yearly. Thus around 200 patients are estimated for possible enrollment in this study.

Previously published studies [2, 17, 21, 22] have shown a reduction of 30–60% in use of CXR. We calculate that a sample size of 55 patients per arm will be needed to provide 80% power (two-sided alpha level of 0,05), and to detect at least 20% reduction in the investigational group.

10.2 Statistical Analysis

The primary analysis of this study is designed according to the intention-to-treat principle, and thus analyzed to their originally assigned group. Patients who are subjected to group cross-over will be analyzed in a subgroup. The subgroup analysis will investigate the sensitivity and specificity of the interventional group endpoints, as well as agreement with control group outcomes. Additionally, the subgroup analysis will semi-quantitatively investigate patient satisfaction, when comparing the two methods of examination.

10.2.1 Pre-planned Subgroup Analysis

We will compare patient satisfaction as secondary outcomes in this trial for patients subjected to crossover from investigational to control group, regardless of reason. The rationale for this being an opportunity to both compare the principal outcomes of the two methods of examination, and to evaluate the psychometric effects of the same.

10.2.2 Significance

A two-sided P-value of less than 0.05 will be considered statistically significant.

10.2.3 Interim Analysis

An interim analysis will be conducted after patient no. 20 has been discharged from the hospital. This will be in accordance with the charter for independent Data Monitoring and Safety Committee (DMSC).

10.2.4 Early Stopping Criteria

The DMSC recommend pausing or stopping of the trial if the in-group differences in primary outcome, SARs or SAEs can be found or are suspected in the interim analysis. This will also apply if the continuing the trial clearly compromises patient safety. After pausing or stopping of the trial, a second analysis will be made based on the underlying reasons.

10.2.5 Accountability Procedure for Missing Data/Population for Analysis

Should less than 5 % of data be missing on either primary or secondary outcomes, a complete analysis will be performed without input of missing data. Missing data more than 5 % will warrant rational assessment of the pattern of missing data, mainly if the loss of data is random or not.

11 Quality Control and Quality Assurance

11.1 Monitoring of Intervention Group

An interim analysis for monitoring of adverse events, including missed diagnosis, will be conducted when 55 patients have been enrolled in the study. All recorded data on paper CRF and collected digital images will be reviewed by a study monitor of the patient safety monitoring board. The monitor will verify data entries against existing source documents for accuracy and content.

11.2 Subject Log

A ‘subject log’ of screened and included subjects will be kept on file by the investigator according to the Consolidated Standards of Reporting Trials (CONSORT). This will help the investigator envisage an accurate ‘rate track’ and estimate the number of patients who did not meet inclusion criteria. Should the rate fall below appreciable levels, the investigators will be able to identify reasons and remedial actions could be undertaken.

12 Legal and Organizational Aspects

12.1 Finance

The principial investigator of the trial is scheduled to part time for research as per agreement with the clinic where this trial is conducted. Apart from this, the trial is considered to be without need of further financing.

12.1.1 Trial Funding

This trial receives no additional funding.

12.1.2 Compensation

Patients enrolled in this trial will not be eligible for compensation.

12.2 Insurance

Participants in this trial will have insurance as part of the standard hospital care insurance in Sweden.

12.3 Plan for Publication, Authorship and Dissemination

12.3.1 Publication Authorship

In advance of first enrollment, this trail will be registered on www.clinicaltrials.gov, along with the final protocol and description of design and plan for analysis. Upon completion of the trial, a manuscript of trial results will be submitted for peer-review publication to a relevant clinical journal.

Listing of authors will be as follows: S. Ullmark will be the first author, J. Jakobsson the second, J. Engström the third, and E. Thorén the fourth. L. H-J will be the last and corresponding author. Authorship will be granted in accordance to the Vancouver definitions depending on personal input in the trial.

12.4 Intellectual Property Rights

The sponsor and main doctoral supervisor for this trial is L. Hellgren-Johansson. The initiative for this trial was taken by the principial investigator S. Ullmark and L. H-J together with doctors affiliated with the doctoral candidate (S. U.), the clinic and other ICUs at the hospital. Thus, no further claims to intellectual property rights are warranted.

12.5 Organizational Framework

This trial is a part of a doctoral candidate thesis for the principial investigator, Sebastian Ullmark.

12.6 Trial Timeline

Autumn/winter 2023: Ethical and formal governance approval of applications and other trial preparations

January 2024: First patient enrolled

May 2024: Preliminary time for interim analysis

September 2024: Last patient enrolled

Winter 2024: Data analysis and submission for publication

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15 Appendices

Appendix 1: Timing of Data Collection

	Surgical ward		Surgery	PACU	Surgical ward		Follow-up
	Admittance	Pre-op	POD 0		2-4 hrs. after chest tube removal	Pre-discharge	
In- /exclusion criteria							
Informed consent							
LUS							
CXR							
Ventilatory parameters							
Physiological parameters							
Inter-observer analysis							
Patient Satisfaction							