

Uni-portal and three-portal video-assisted thoracic surgery pulmonary lobectomy for early stage lung cancer (UNIT trial): study protocol of a single-center randomized trial

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Abstract

Background

Video-assisted thoracoscopic surgery (VATS) lobectomy is currently the recommended approach for treating early-stage non-small cell lung cancer (NSCLC). Different VATS approaches have been proposed so far, and the actual advantages of one technique over the other are still under debate. The aim of our study is to compare postoperative pain and analgesic drug consumption in uniportal VATS and triportal VATS for pulmonary lobectomy in early-stage lung cancer patients.

Methods

This study is a single-centre, prospective, two-arm, parallel-group, randomized controlled trial. It is designed to compare uniportal video-assisted thoracic surgery (u-VATS) and three-ports video-assisted thoracic surgery (t-VATS) in terms of post-operative pain. The trial will enrol 120 patients with a 1:1 randomization. The primary outcome is the assessment of analgesic drug consumption. Secondary outcomes are postoperative pain measurement, evaluation of postoperative pulmonary function, and metabolic recovery after pulmonary lobectomy.

Discussion

The choice of which VATS approach to adopt for treating patients undergoing pulmonary resection mostly depends on the surgeon's preferences; therefore, it is hard to prove whether one VATS technique is superior to the other. Moreover, postoperative analgesic protocols vary consistently among different centres. To date, only a few studies have evaluated the effects of the most popular VATS techniques. There is no evidence about difference between multi-ports VATS and u-VATS in terms of postoperative pain. We hope that the results of our trial will provide valuable information on the outcomes of these different surgical approaches.

Trial registration

ClinicalTrials.gov. NCT03240250; registered 08/07/2017; retrospectively registered; <https://clinicaltrials.gov/ct2/show/NCT03240250?term=NCT03240250&draw=2&rank=1>

Background

Currently, video-assisted thoracoscopic surgery (VATS) lobectomy is the recommended approach for treating early-stage non-small cell lung cancer (NSCLC). In 2013, the American College of Chest Physicians indicated VATS as their preferred technique over open surgery (grade 2C) [1]. It is a current opinion that VATS lobectomy is associated with a decreased risk of adverse events, less pain, and shorter length of stay when compared to open surgery [2]; these assumptions are validated by systematic reviews and meta-analyses, even though most of those trials were not randomized [3,4]. At present, significant differences among VATS surgical approaches specifically lie in the numbers of employed

trocars and in the type of utility incisions; in addition, some unusual techniques have been described, such as the transcervical [5], the subxiphoid uniportal [6], and the microlobectomy [7]. The three-port anterior approach described by Hansen (t-VATS) [8] is currently the most commonly adopted technique [9], because of the optimal access on the hilum, low mortality and proven oncological validity [10,11]. In 2011 Gonzales Rivas published the first results on pulmonary lobectomy performed via uniportal VATS (u-VATS) [12]. This technique has progressively gained consensus, initially in Asian countries, thereafter in Europe [13]. The debate on the actual advantages of u-VATS over t-VATS is still open [14]. A decrease in postoperative pain and paraesthesia has been reported in minor procedures [15] while to date, there is no adequate evidence on postoperative pain after pulmonary lobectomy. The only randomized study, comparing u-VATS with the “multiports” VATS lobectomy, did not reveal statistically significant differences in terms of postoperative pain [16]. An expert consensus statement in 2019 suggested that u-VATS lobectomy might reduce early postoperative pain and analgesic requirements compared with multiport VATS (m-VATS) [17]. The same group of Authors conducted a systematic review and meta-analysis: pooled analyses showed significantly reduced pain according to visual analog scale (VAS) scores in u-VATS patients compared to m-VATS patients on postoperative days 1, 3, 7 and 30. Only two studies including 240 patients reported on the analgesic use: u-VATS patients used analgesics for significantly fewer days per month than m-VATS patients did [18]. The aim of our study is to compare the effects of u-VATS and t-VATS for pulmonary lobectomy in early-stage lung cancer patients, in terms of postoperative pain.

Methods

Trial design

The study was designed as a single-centre, prospective, two-arm, parallel-group, randomized controlled trial.

The protocol (Version 1.0_13/12/2016) is reported in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines following the SPIRIT schedule (Figure 1), trial flow chart (Figure 2) and Checklist (Additional file 1). The study was registered on ClinicalTrials.gov: NCT03240250. The fundamental hypothesis is that u-VATS could cause lower postoperative pain than t-VATS pulmonary lobectomy for early-stage lung cancer patients. Our hypothesis is based on a simple premise: fewer chest incisions correspond to less pain. This hypothesis is tested out by using analgesic drug consumption as an objective measurement of postoperative pain.

Given an estimated difference of analgesic drug consumption of 20%, the calculated sample-size is 120 patients (60 patients each arm), with a 1:1 randomization.

We planned to perform an ‘interim analysis’ once a total number of at least 60 randomized patients, dropouts excluded, is reached. The ‘interim analysis’ will be performed to ensure the safety of the study and to evaluate any significant outcome-related differences between the two techniques that would make the study unnecessary. The surgical staff routinely analyzes the complication rates of every surgical

procedure, in a dedicated monthly meeting. From this analysis, if a higher complication rate will be detected in one arm over the other, a data and safety monitoring board (DSMB) will be set up. Furthermore, to protect patients' safety, could be set up during the study, if necessary. All items from the WHO clinical trial registry can be found within the protocol.

Eligibility criteria

All consecutive patients referred to our centre, the Thoracic Surgery Unit of the University Hospital Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan (Italy) will be screened by one of two designed member of our surgical staff, according to inclusion and exclusion criteria. Before enrolment, each patient will receive detailed information regarding the study protocol. A specific informed consent regarding the participation to the trial, the randomization, and the surgical incisions will be obtained by a staff surgeon from each participant, after an adequate explanation of the benefits and risks of the study.

The study was approved by the Ethics Committee of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy on 21 February 2017, (reference number 86_2017), before the trial registration on ClinicalTrials.gov.

The study will be carried out in accordance with the Helsinki Declaration.

Inclusion criteria

- Age between 30 and 80 years
- Both genders
- Surgically resectable (R0) non-small cell lung cancer (NSCLC), with cytological or histological diagnosis or clinically suspected, with a diameter lower than 5 cm
- Clinical stage I and II NSCLC
- Patient with American Society of Anaesthesiologists (ASA) score I, II or III
- Written informed consent (ICF) signed by the patient

Exclusion criteria

- Inability to comply with the study procedure
- N2 or N3 clinical nodal involvement of disease
- Induction chemotherapy before surgery
- Chest wall involvement
- Previous thoracic surgery (any type)
- High-grade pleural adhesions
- Renal, liver, or cardiac failure

- Severe chronic obstructive pulmonary disease (COPD), bronchial asthma or interstitial lung disease (ILD)
- Coagulation disorders
- Allergy to analgesic drugs included in the study protocol
- Chronic use of analgesics, opioids, or steroids
- Wedge resection, sleeve lobectomy or pneumonectomy
- Re-intervention after VATS lobectomy

Outcome definitions and measures

Primary outcome

- Postoperative pain after u-VATS and t-VATS, measured by means of total analgesic consumptions, normalized to morphine milligrams, recorded within the 7 days following the operation

Secondary outcomes

- Postoperative pain measured by a numeric rating scale (NRS) after 2, 6, 12 , and 24 hours and on postoperative days (POD) 2, 3, 4, 5, and 30. A pain score will be assigned to each patient after the total amount of NRS is determined. A mean pain score will be calculated and compared between the two groups.
- Evaluation of respiratory function, measured by pulmonary function tests (PFTs) as basal spirometry on POD 7 and POD 30, compared with preoperative measures. Forced Vital Capacity (FVC) and Forced expiratory volume at 1 second (FEV1) will be considered in litres and percentage as measured by PFTs. Pre-operative and post-operative measurements will be weighted and normalized for the number of lung segments removed during each lobectomy. The mean differences between pre- and post-operative values will be calculated and compared between the two groups.
- Evaluation of functional and metabolic recovery, measured by metabolic Holter, a multidetection tool recording patients' physiological data and energy consumption. We will measure physiological data at rest (heart and respiratory rate, arterial blood pressure) and the level of physical activity of the patient, expressed in metabolic equivalents (METs). Means of METs will be calculated and compared between the two groups.
- Intraoperative parameters, calculated by means and percentage:
 - Intraoperative time: measurement of time in minutes from skin incision to the closure of the chest (skin to skin)
 - Intraoperative bleeding: measurement of the total amount of bleeding during the operation expressed in millilitres
 - Total number of resected lymphnodes
 - Conversion rate from VATS to open thoracotomy (total number and percentage)
- Postoperative parameters, calculated by means and percentage:

- Postoperative air leaks (days of air leaks)
- Chest drain dwelling time (days)
- Infection of surgical site (total number and percentage)
- Pulmonary complications, including pneumonia, pulmonary embolism, atelectasis (total number and percentage)

Randomization

An individual simple sequence randomization with 1:1 allocation will be generated by a person not involved in the enrolment, using the *random allocation rule* [19] by RandomizeR R software package; the consequent assignment to either of the two arms will be done using closed envelopes. The envelopes will be numerated consecutively, containing a sheet marked with an “U” in case of u-VATS arm or with a “T” in case of t-VATS arm. The allocation of the patient in one or the other arm will be performed in the operating theatre before surgery. The envelope assigned to the patient will be opened by the surgeon during the induction of general anaesthesia before surgery. If the patient is assigned to the u-VATS arm, a uniportal VATS lobectomy will be performed. In case of the assignment to t-VATS group, the surgeon will perform a three ports VATS lobectomy. Given the type of study, patients and investigators cannot be blinded.

Description of surgical procedures

Both surgical procedures, u-VATS and t-VATS, will be performed following the same anaesthesiologic plan. General anaesthesia will be administered, and a double-lumen endobronchial tube will be used to allow single-lung ventilation. Patients will be monitored by standard electrocardiogram (ECG), invasive arterial blood pressure, pulse oximeter, urine catheterization and, if necessary, central venous catheterization. Patients will be positioned in lateral decubitus, contralaterally to the side of surgery and the bed will be flexed to get wide intercostal spaces.

- *u-VATS*: a single, lateral, muscle-sparing, 4 to 5-cm minithoracotomy will be performed through the 4th or 5th intercostal space. No other intercostal incision will be made. All the instruments and camera will be inserted through the minithoracotomy. After pulmonary lobectomy and lymphadenectomy, one intercostal drainage will be inserted through the minithoracotomy [12].
- *t-VATS*: a lateral, muscle-sparing, 4 to 5-cm minithoracotomy will be performed through the 4th or 5th intercostal space. Two additional thoracoscopy ports will be performed in the 7th or 8th intercostal space. The camera and the instrument will be inserted into the pleural space through the minithoracotomy or the thoracoscopy port according to the surgeon's preference. After pulmonary lobectomy and lymphadenectomy, one intercostal drainage will be inserted through the anterior intercostal incision [8].

Description of pre-, intra-, and post-operative anaesthesiologic management

Preoperative assessment was performed according to the European Society of Anesthesiology guidelines for the evaluation of candidates to non-cardiac surgery [20].

After routine monitoring as per the American Society of Anesthesiologists guidelines and peripheral venous cannulation (20-16 Ch PVC catheter), induction of general anaesthesia with fentanyl (1-2 mcg/kg), midazolam (1-2 mg) and propofol (1-3 mg/kg), and muscle paralysis with rocuronium (0.6-1 mg/kg) is achieved. Patients are intubated with appropriately sized left-sided double-lumen endotracheal tube under bronchoscopic guidance. General anaesthesia is maintained with sevoflurane (end-tidal concentration 1.0%-2.0%) to keep the Bispectral Index value between 40 to 60 during the whole surgical procedure, muscle paralysis with sequential rocuronium boluses (0.15 mg/kg), while analgesia is achieved by titrating remifentanyl infusion between 0.05 to 0.15 mcg/kg/min according to autonomic responses to surgical stress. Whenever potential risk factors for malignant hyperthermia are identified, total intravenous anaesthesia with propofol (4-6 mg/kg/h) is induced. Patients' invasive arterial pressure is monitored with radial artery cannulation (3Fr, 5cm catheter). Central venous cannulation is performed only if central venous pressure monitoring is required. A body surface heating device is applied, and pharyngeal temperature monitoring is established with a target temperature of 35.5- 36.5° C.

Ahead skin incision, together with antibacterial prophylaxis, 30 mg ketorolac, and either anti-H2 receptors or proton pump inhibitors are administered. About one hour before surgery termination 0.1-0.15 mg/kg, intravenous morphine is administered together with 1g acetaminophen. For post-operative nausea and vomiting prevention, 4 mg ondansetron are given. Before suturing surgical incisions, an intercostal nerve block is performed by the surgeon on the surgical field by injecting 2-5 mL of 0.375% ropivacaine per intercostal space under thoracoscopic view. Up to 40 mL are administered with a maximum ropivacaine dose of 2mg/kg. After anaesthesia termination, the patient is extubated in the operating room, unless he or she needs protected weaning from mechanical ventilation in the Intensive Care Unit. Immediate post-operative monitoring is performed in the recovery room. If hemodynamic and respiratory function stability is achieved, the patient is transferred to the surgical ward; otherwise, if further monitoring or intensive medical treatment prove necessary, he or she will be transferred to the Intensive Care Unit. Postoperative analgesia is initiated in the recovery room as soon as full recovery of consciousness is observed: intravenous morphine is administered at a rate of 1 mg/h for the first 6 hours postoperatively. 6 hours after surgery completion and every 4 hours thereafter, nurses record the dynamic NRS for pain evaluation. If at any evaluation time-point the NRS value is below 4, morphine infusion is halved; if NRS value is between 4 to 6, morphine infusion rate is maintained, while, if NRS value is higher than 6, a bolus of 1-2 mg morphine is administered. Parallel administration of intravenous acetaminophen 1 g every 6 hours and ketorolac 30 mg every 8 hours is performed for the first 3 post-operative days.

Postoperative management and follow-up

The patient will be treated during postoperative course as the standard of care requires, including short-term intravenous antimicrobial prophylaxis, early mobilization, and respiratory physiotherapy. The chest

tube will be removed when the total amount of pleural fluid will be <300 mL/day and no air leaks is detectable.

Patients will be followed up after discharge at POD 7 with clinical examination and PFTs (spirometry) and POD 30 with a clinical examination, NRS pain score, PFTs and chest X-rays. During the study period, any relevant concomitant treatment will be authorized.

Drop out/Study termination

Every patient has the opportunity to drop out of the study at any time. The participant's choice will not compromise their medical treatment that he or she will receive as the standard of care requires. Patients who will drop out, will not be displaced to other Units. Due to the relative short follow-up time required (30 days), we expect a small percentage of patient who will be lost at follow-up (about 1-2%), since patients are usually seen one month after the discharge. No specific plans are scheduled for participant retention and prevention of loss-to-follow-up. If the percentage of drop out will be < 5% we will continue the recruitment and consider the study valid.

Statistical analysis

All the statistical analyses will be performed by blinded analysts. Periodical checking of the input data will be performed in order to verify the completeness and consistency of the dataset. Checks on the consistency and plausibility of the reported data will be carried out before data analysis. The study is powered based on its primary outcome. The sample size was calculated considering a 2-sided t-test for difference between two independent means, according to the following assumptions: normal distribution for the primary outcome, Choen's d effect size = 0.55 (obtained after a revision of medical reports), power $(1-\beta) = 0.85$ and $\alpha = 0.05$ [20]. The sample size computation was performed using the R software version 3.2.2 [22]. We have planned to perform an "interim analysis" once a total number of at least 60 randomized patients without dropouts is reached. The 'interim analysis' will be performed in order to ensure the safety of the study and to evaluate any significant outcome-related difference between the two techniques that would advise against completing the study. Furthermore, to protect patients' safety, a data and safety monitoring board (DSMB) could be set up during the study, if necessary.

We will propose two analysis sets: the intention-to-treat set, which would consider all patients randomized regardless of whether they received the randomized treatment, and the 'per protocol' analysis set, excluding patients for intra-operative reasons (i.e.: massive pleural adhesion, conversion to open surgery). The rationale for a 'per protocol' analysis is due to the fact that intra-operative complications have a significant impact on pain which is the primary outcome of our study.

The effect that any missing data might have on results will be assessed via sensitivity analysis of augmented data sets. Dropouts (essentially, participants who withdraw consent for continued follow-up) will be included in the analysis using Bayesian Multiple Imputation by Chained Equations (MICE).

Data collection and results dissemination

Patients will be enrolled by a team physician, and their data will be collected in a paper-based Case Report Form (CRF) designed by study staff during pre and postoperative course and until 1 month after surgery.

CRFs will be transferred in a password-protected Microsoft Excel® spreadsheet with an ID number assigned to every consecutive enrolled patient. The paper-based CRFs and the electronic database will be kept locked up at the Thoracic Surgery and Lung Transplant Unit of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan. The partial and final dataset will be available to the investigators at any time after a request submitted to the Principal Investigator. There are no plans for sharing data from the trial. The trial results will be disseminated in meeting communications and scientific publications. The Authorship policies will be shared with the investigators.

Risks and benefits of the study

Since both surgical techniques (t-VATS and u-VATS) are used in the current clinical practice, patients will not be exposed to any risk besides those typically entailed in VATS lobectomy. For this reason there are no additional adverse events that might be expected in the study. We will use the US National Cancer Institute Common Terminology Criteria for Adverse Events 4.1 (CTCAE version 4.1) in order to describe postoperative complications. All the complications will be registered on patient CRFs.

Discussion

The choice of one VATS approach over the others for patients undergoing pulmonary resection largely depends on the experience of each surgeon; therefore, it is hard to prove whether a technique is more efficient than the other, especially in terms of postoperative pain. Moreover, postoperative analgesic protocols vary considerably among different centres. So far, only a few studies have evaluated the effects of the most popular VATS techniques, the t-VATS and the u-VATS. In 2005, a paper by Jutley et al. retrospectively compared the postoperative pain scores in patients undergoing t-VATS or u-VATS for the treatment of spontaneous pneumothorax, using a visual analog scale (VAS) from 0 to 4. They concluded that post-operative pain and paraesthesia incidence was lower in the u-VATS group, despite the cohort of patients being limited [23].

Recently, we have published an observational, retrospective, multicentre study on data collected in the Italian VATS Group Database, evaluating lobectomies performed for clinical stage I–II NSCLC, by u-VATS and t-VATS: u-VATS lobectomy seemed to entail a higher risk of moderate/severe pain on postoperative days 2 and 3 [9].

The only randomized study comparing u-VATS with the 'multiports' VATS lobectomy was a single monocentric trial published by Perna et al. No statistically significant difference between the two groups in terms of postoperative pain was recorded. Nevertheless, one might argue that the sample size was rather under-dimensioned, mainly because the 'multiports' group included patients who underwent two different procedures: the Duke two-port technique and the Copenhagen t-VATS approach [16].

The proposed trial will broaden current knowledge of this area by investigating the difference between the t-VATS and the u-VATS in terms of postoperative pain. We have based our hypothesis on a simple premise: u-VATS is less painful than t-VATS because “one incision is less painful than three”. From a strictly logistical point of view, manipulation of the intercostal space is inevitable while employing every VATS technique, as any additional access to the service minithoracotomy can only increase the patient's amount of pain. Unlike other studies that compared multiports-VATS (including two, three and more ports VATS) to u-VATS, our own study compared two single techniques: in our opinion, this is a methodological advantage, reducing possible confounding bias.

A challenging aspect of any clinical trial is the evaluation of pain suffered by patients. Several clinically tested and validated pain scales have been proposed so far; these try to meet the criteria of objectivity, comprehensibility, and reproducibility. Among the most frequently used pain scales the Verbal Rating Scale is based on patients' answers to verbal questions of health care professionals; this scale measures pain intensity only and is subject to discrepancies depending on how each patient understands “mild,” “moderate,” and “severe” pain. Visual Analog Scale (VAS) is probably the most used pain assessment tool because it is simple to administer, rapid, and easy for patients to understand. However, the VAS likely undervalues pain as a “biopsychosocial” experience and furthermore only measures pain intensity in a specific moment. For our trial, we have decided to use analgesic drug consumption as an objective measure of the “entire pain” suffered by patients during the first postoperative week. By normalizing the amount of the different painkillers used during the first postoperative week to morphine milligrams we will obtain cumulative morphine consumption, which is a numeric parameter properly that statistics can properly manage [24].

A secondary endpoint of our study is the evaluation of early postoperative respiratory function, measured by pulmonary function tests. There is no doubt that the greatest impact on respiratory function is attributable to the parenchymal sacrifice following the pulmonary lobectomy itself; nevertheless, the type of surgical insult of the chest wall is significant as well [25]. Hence, multiple chest wall incisions can potentially impact the decreased respiratory function more than a single incision.

In conclusion, the results of this project will broaden current knowledge of the effects of two different VATS approaches to pulmonary lobectomy for lung cancer.

Abbreviations

ASA: American Society of Anesthesiologists; COPD: chronic obstructive pulmonary disease; CRF: case report form; CTCAE: Common Terminology Criteria for Adverse Events; DSMB: data and safety monitoring board; ECG: electrocardiogram; ICF: informed consent form; ILD: interstitial lung disease; NRS: numeric rating scale; NSCLC: non-small cell lung cancer; METs: metabolic equivalents; MICE: Multiple Imputation by Chained Equations; m-VATS: multi-port Video-Assisted Thoracic Surgery; PFTs: pulmonary function tests; POD: postoperative day; PVC: peripheral venous catheter; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; t-VATS: three-port Video-Assisted Thoracic Surgery; u-VATS:

uniport Video-Assisted Thoracic Surgery; VAS: visual analog scale; VATS: Video-Assisted Thoracic Surgery;

Declarations

Trial status

The study started in February 2017. Patients have been enrolled since March 2017 and will be enrolled until September 2020. The study will be interrupted once the sample size of 120 patients enrolled is reached.

Ethics approval and consent to participate

The study was approved by the Ethic Committee of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan (Italy), reference number 86_2017. If necessary, any substantial protocol modification or amendment will be submitted to the Ethics Committee after approval by the investigators.

All patients enrolled will sign a specific consent form (ICF), after being thoroughly instructed in person and having received all relevant information regarding the study in writing, according to Helsinki Declaration. Every ICF will be signed by the patient and a physician before data collection.

Consent for publication

No patient data. Not applicable

Competing interests.

All authors have no competing interests to declare

Funding

There is no funding for this trial

Authors' contributions

PM and DT designed the study. DT, GB, and MN wrote the study protocol. PM, AM, JF and DT wrote the manuscript. AM, RC, FD are enrolling patients and collecting data. EP is collecting data. AP, LR, IR contributed to draft writing and editing. All authors read and approved the final manuscript.

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Figures

TIMEPOINT (days)	STUDY PERIOD												
	Enrolment	Allocation	Post-allocation (Post-operative day number)										Close-out
	-1	-1	0	1	2	3	4	5	6	7	15	30	12/2020
ENROLMENT:													
Eligibility screen	X												
Informed consent	X												
Allocation		X											
INTERVENTIONS:													
Arm 1 [u-VATS]			X										
Arm 2 [t-VATS]			X										
ASSESSMENTS:													
Demographics data	X	X											
Intraoperative data			X										
Analgesic consumption				X	X	X	X	X	X	X			
Pain (NRS)			X	X	X	X	X	X				X	
PFTs										X		X	
PAL										X	X		
Complications			X	X	X	X	X	X	X	X	X	X	

t₀: day of surgery; t₁: post-operative day (POD) 1; t₂: POD2; t₃: POD3; t₄: POD4; t₅: POD5; t₆: POD6; t₇: POD7; t₈: POD8; t₁₅: POD₁₅; t₃₀: POD₃₀; u-VATS: uniportal video-assisted thoracic surgery lobectomy; t-VATS: three-portal video-assisted thoracic surgery lobectomy; NRS: numeric rating scale; PFTs: pulmonary function tests (spirometry); PAL: persistent air leaks.

*Recommended content can be displayed using various schematic formats. See SPIRIT 2013 Explanation and Elaboration for examples from protocols.

**List specific timepoints in this row.

Figure 1

Study process schedule (according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines)

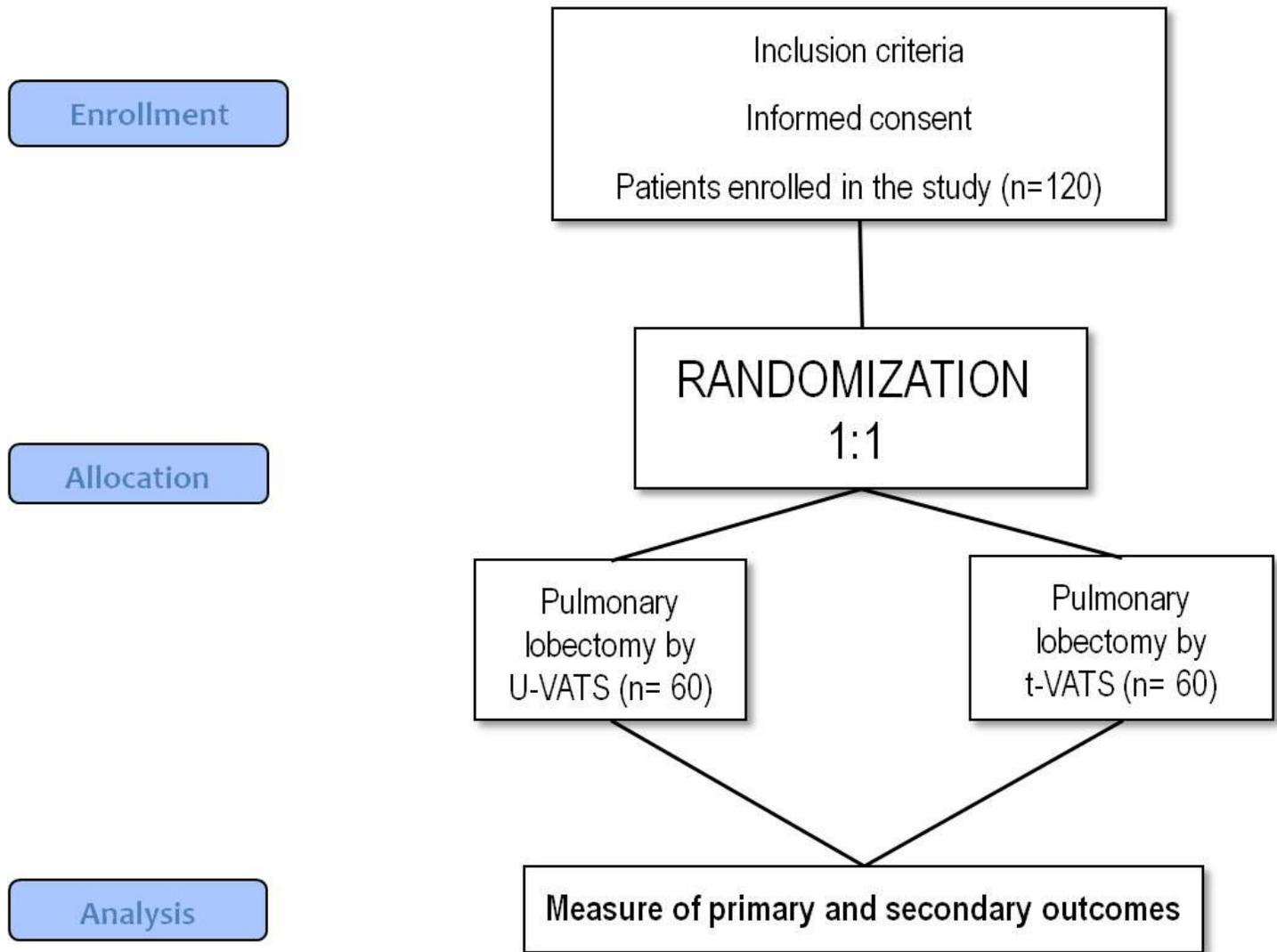


Figure 2

Trial flow chart

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CaseReportFormSupplementarymaterial.doc](#)
- [InformedConsentForm.pdf](#)
- [SPIRITchecklistrevised.doc](#)