

DEPARTMENT OF MEDICINE
UNIVERSITI KEBANGSAAN MALAYSIA

A Pilot Randomized Controlled Trial Comparing Safety and Feasibility of Medical Thoracoscopy using Single-use Flexible Bronchoscope versus SemiRigid Pleuroscope among Hospitalized Patients with Pleural Effusion (FLEXPLEUR2)

VERSION 1.0
DATE : 1.7.2026
RESEARCH ID : JEP-2026-204

TABLE OF CONTENT

CHAPTER 1: INTRODUCTION
1.1 Research Background
1.2 Problem Statement
1.3 Research Questions
1.4 Research Hypotheses
1.5 Novelty

CHAPTER 2: RESEARCH OBJECTIVES
2.1 Research Objectives
2.1.1 General
2.1.2 Specific
2.2 Significance of Research

CHAPTER 3: LITERATURE REVIEW

CHAPTER 4: METHODOLOGY
4.1 Type of Study
4.2 Study Design
4.2.1 Period of Study
4.2.2 Study Setting
4.2.3 Sampling Population
4.2.4 Inclusion Criteria
4.2.5 Exclusion Criteria
4.3 Study Protocol and Data Acquisition
4.4 Sample Size
4.4.1 Sample Size Calculation
4.4.2 Study Sample Size
4.5 Patient/Sample Collection Pathway
4.6 Statistical Analysis
4.7 Dummy Tables

CHAPTER 5: OPERATIONAL TERM DEFINITION
5.1 Medical Thoracoscopy
5.2 Flexible Bronchoscope
5.3 Semi-rigid Pleuroscope
5.4 Diagnostic Yield
5.5 Complication Type
5.6 Complication Rate
5.7 Duration of Procedure

CHAPTER 6: GANTT CHART

CHAPTER 7 : FINANCIAL IMPLICATION

CHAPTER 8: PATIENT INFORMATION SHEET

CHAPTER 9 : PATIENT CONSENT

CHAPTER 10 APPENDICES

CHAPTER 11: REFERENCES

ABBREVIATION

- BHT Bed Head Ticket
- HCTM UKM Hospital Canselor Tuanku Muhriz UKM
- MT Medical Thoracoscopy
- UKMMC Universiti Kebangsaan Malaysia Medical Center
- VATS Video-Assisted Thoracoscopic Surgery

CHAPTER 1 INTRODUCTION

1.1 RESEARCH BACKGROUND

Pleural effusion is a common problem in hospital patients. It may arise from a wide range of diseases. There is a multitude of recognised causes of pleural effusion, and in addition, other pleural conditions such as pleural thickening and pneumothorax represent a significant burden to the healthcare system and to patients. However, the diagnosis of this condition may sometimes be difficult. In pleural effusions undiagnosed by thoracocentesis, closed pleural biopsy increases the yield by ~10% and 40%, respectively, in malignant and tuberculous pleural effusions, whereas the diagnostic yield of thoracoscopy is ~93% in both malignant and tuberculous pleural effusions [1]. Hence, medical thoracoscopy (MT) (pleuroscopy) is the gold standard in the diagnosis of pleural effusion and it is indicated when less invasive tests have failed [2]. MT is a procedure in which the pleura is directly and visually examined. An endoscope is inserted into the intercostal space by creating a pneumothorax with an incision through the chest wall. The pleural space and its lining can be inspected and therapeutic interventions performed.

There are two different techniques that can be performed for diagnostic and therapeutic thoracoscopy. One method recommends a single-entry site, the use of a usually 9-mm rigid thoracoscope (or of a semi-rigid/semi-flexible 7-mm pleuroscope) with a working channel for accessory instruments and an optical biopsy forceps, both performed under local anaesthesia. The other method requires two entry sites: one for a 7-mm trocar for the examination telescope, and the other for a 5-mm trocar for accessory instruments including the biopsy forceps, and is usually performed with conscious sedation or general anaesthesia [3].

In the trained hands of a pulmonologist, MT is a safe and effective procedure for diagnosing and treating multiple pleural diseases [4]. Valsecchi et al reported a pathological diagnostic yield of 71% over a span of 30 years in around 2000 patients[5]. The unfamiliarity of the pulmonary physician with the rigid instrument and familiarity with the flexible bronchoscope has led various investigators to attempt thoracoscopy even with a fibreoptic bronchoscope [6].

The use of a flexible fibreoptic instrument to examine the pleural space was reported by Senno et al in the 1970s in the United States. Studies showed that flexible bronchoscope, when used as a thoracoscope, maintains a clear optical field by allowing concurrent suctioning, which is analogous to the suction techniques used during flexible bronchoscopy [3] and better views at the apex and paravertebral gutters [7]. This method is, therefore, considered to be useful for surgeons or physicians with experience in chest drainage and flexible bronchoscopy as well as safe and well tolerated with a minimal degree of discomfort and expense [8].

1.2 PROBLEM STATEMENT

MT service in Malaysia has been available since 2005. Currently, only a few government tertiary hospitals offer such services. These centres include Hospital Tuanku Ampuan Afzan (HTAA), Hospital Canselor Tuanku Muhriz (HCTM), Hospital Queen Elizabeth Kota Kinabalu, Kuala Terengganu State Hospital and Penang State Hospital [8]. In view of the limited number of government tertiary hospitals offering the service, often the accurate diagnosis of pleural diseases can be challenging. Conservative estimates suggest that 25% of patients seen in a general pulmonologist's practice involved the pleura. Of these cases, 25% were unable to be attributed to a specific diagnosis, even after thoracocentesis and closed pleural biopsy [9, 10].

One of the disadvantages of rigid thoracoscopy is its potentially increased discomfort to the moderately sedated patient. To thoroughly examine the pleural space, the rigid metal tube needs to be directed in different angles and can apply significant amount of pressure on the ribs, as it is pointed towards different locations in the hemithorax. A semi-rigid pleuroscope has the "look and feel" of a flexible bronchoscope, and thus in a setting whereby semi-rigid pleuroscope is not available, it may be an alternative to a more invasive rigid pleuroscopy or VATS. Semi-rigid pleuroscope has almost similar design and handling of flexible bronchoscope, which means that physicians can perform the procedure analogous to flexible bronchoscopy. In addition, it is capable of maintaining a clear visual field by allowing concurrent suctioning, which is identical to the suction techniques used during flexible bronchoscopy, and it may overcome a limited view by manoeuvring its flexible tip in different directions and around adhesions. Its flexible tip facilitates the homogeneous insufflation of talc (*via* a catheter), introduced through the working channel, into all areas of the parietal and visceral pleura [3].

In resource-rich environments, medical pleuroscopy with a semi-rigid pleuroscope or rigid thoracoscope on these undiagnosed patients is the preferred step because of its high sensitivity in malignant and tuberculous pleural effusions [11]. Such a procedure has high diagnostic yield but poses specific health care utilisation demands that are not universally available. If semi-rigid pleuroscopy is not available, MT using a flexible bronchoscope might provide a diagnosis when other less invasive measures have failed to do so, reducing the need for the more invasive and much more expensive thorascopy as well as reducing delays in diagnosing pleural diseases.

The true cost of semi-rigid thoracoscopy in Malaysia is not clearly documented. An economic evaluation reported the mean procedure-related cost of semi-rigid thoracoscopy as $2,815 Canadian dollars (95% Confidence Interval $2,010 to $3,620) compared to video-assisted thoracoscopic surgery of $7,962 Canadian dollars (95% Confidence Interval $7,134 to $8,790) in patients with undiagnosed pleural effusions. Since all video-assisted thoracoscopic surgery was conducted in the hospital whereas 68% of semi-rigid thoracoscopy was performed as outpatient procedures, the longer hospital stay associated with video-assisted thoracoscopic surgery may have contributed to some of the difference in procedure cost [12].

Previous FLEXPLEUR study that was conducted has shown that flexible and semi-rigid pleuroscopy have comparable diagnostic yield and similar intraprocedural safety[13].

However, there are no study looking at the diagnostic yield of performing pleuroscopy using disposable flexible bronchoscopy

This study would like to propose the following paradigm:

1. Diagnostic yield of MT using disposibe flexible bronchoscope is no different to using conventional gold standard semi-rigid pleuroscope.
2. Complication rate and profile in MT using Single-use flexible bronchoscope is no different than those using semi-rigid pleuroscope.

1.3 RESEARCH QUESTION

Can MT using a disposable flexible bronchoscope be used as an alternative method to a semi-rigid pleuroscope for diagnosis of pleural effusion with a comparable outcome?

1.4 RESEARCH HYPOTHESES

1 Medical thoracoscopy using a single-use flexible bronchoscope is feasible, defined by successful entry into the pleural space, adequate pleural visualization, successful pleural biopsy acquisition, and completion of the procedure without conversion to conventional semi-rigid pleuroscopy.

- There is no significant difference in the total duration of the procedure (in minutes) between medical thoracoscopy performed using the single-use flexible bronchoscope and the conventional semi-rigid pleuroscope.
- Medical thoracoscopy using a single-use flexible bronchoscope is operationally feasible, showing no significant difference in procedural success rates—defined as successful entry into the pleural space, adequate visualization, and successful tissue collection without requiring device crossover—when compared to the conventional semi-rigid pleuroscope.
- The immediate procedural cost-utilization and disposable hardware expenditures associated with the single-use flexible bronchoscope arm will be different from (or lower than) the conventional semi-rigid pleuroscope arm.
- There is no significant difference in the preliminary baseline diagnostic yields or the 48-hour post-procedural complication rates and profiles between the single-use flexible bronchoscope group and the conventional semi-rigid pleuroscope group

1.5 NOVELTY

This is first study that we know of that has attempted to evaluate the diagnostic yield of medical thoracosopy using disposable flexible bronchoscope and its complications. This study may be used to see whether there is a suitable alternative for respiratory physician to safely diagnosed pleural disease after a failed non-invasive procedure. While conventional medical thoracoscopy is the more expensive procedure, the true difference in procedure-related costs associated with disposable flexible bronchoscope compared to semi-rigid pleuroscope is unknown due to the lack of cost-analysis study. Perhaps this study can provide the basis for future study to analyse the true cost-benefit of using disposable flexible bronchoscope in medical thoracoscopy.

CHAPTER 2 RESEARCH OBJECTIVES

2.1 GENERAL OBJECTIVE

To evaluate the feasibility rate (in percentage) of medical thoracoscopy using a single-use flexible bronchoscope compared with the conventional semi-rigid pleuroscope

Feasibility is defined as:

I. **Recruitment** feasibility – Proportions of patient who consent and are randomized
II. **Randomization** feasibility – Proportion of patients who receive their allocated intervention
III. **Protocol adherence** – Proportion of patients managed according to the assigned intervention
IV. **Procedure Feasibility** - Ability to successfully perform the key procedural components of pleuroscopy, including safe entry into the pleural space, adequate visualization of the pleural cavity, successful acquisition of pleural biopsy
V. **Procedural completion** – Proportion of procedures successfully completed using the allocated instrument
VI. **Crossover rate** – Proportion requiring crossover from allocated instrument due to technical difficulty
VII. **Follow up completion** – Proportion with complete outcome date up to 48 hour after procedure

2.2 SPECIFIC OBJECTIVES

- To compare the **difference in procedure duration (in minutes) between the single-use flexible bronchoscope and the conventional semi-rigid pleuroscope to evaluate time-efficiency.**
- To compare the **procedural success rate** between the two arms, defined as successful entry into the pleural space and adequate tissue sample collection without needing to switch devices.
- To compare the d**ifference in immediate procedural and disposable hardware costs between Single-Use Flexible Bronchoscope and Conventional Semi-Rigid Pleuroscope**.
- To compare the **diagnostic yield rate (in percentage)** between Single-Use Flexible Bronchoscope and Conventional Semi-Rigid Pleuroscope
- To measure the **incidence of immediate treatment related adverse events (in percentage) within 48 hours** between Single-Use Flexible Bronchoscope and Conventional Semi-Rigid Pleuroscope

2.3 SIGNIFICANCE OF RESEARCH

This research proposal is important to improve the diagnosis of hospital patients presenting with pleural effusion in Malaysia. Semi-rigid pleuroscope is expensive and not widely available, whereas disposable flexible bronchoscope is more readily available and can be used as an alternative for medical thoracoscopic pleural biopsy. There is no previous study looking at diagnostic yield comparison between disposable flexible bronchoscope and semi-rigid pleuroscope. This study could potentially serve as a feasibility study that can help future investigators prepare for full-scale research leading to intervention. As medical thoracoscopy is already an established standard-of-care procedure with high diagnostic yield, this study does not evaluate the necessity of thoracoscopy itself, but rather assesses whether a single-use flexible bronchoscope can serve as a feasible alternative platform for performing the procedure.

CHAPTER 3 LITERATURE REVIEW

Thoracoscopy was first introduced by Hans-Christian Jacobaeus in 1910 and since then its application is accepted in particular for the diagnosis of pleural effusion and for pleurodesis of malignant effusion, whereas its use in the management of spontaneous pneumothorax has been highly effective [14]. Thoracoscopy can be performed using either video-assisted thoracoscopic surgery (VATS) or MT. MT is performed under local anaesthesia and conscious sedation, whereas VATS requires general anaesthesia and single-lung ventilation. For a diagnostic pleural biopsy, VATS is rarely required because MT is highly efficacious and cost-effective.

Flexible bronchoscopes have already been used for thoracoscopies based upon several case reports from 1975 which described this technique [15]. Presumably, these flexible bronchoscopes were used because there were no suitable instruments available during the time. In the early advent of MT, the use of flexible bronchoscope has a conflicting finding. Davidson et al compared rigid thoracoscope and fibreoptic bronchoscope (used as a flexible thoracoscope) and the diagnostic adequacy of biopsy specimens obtained with the two instruments. Flexible bronchoscopes failed to show equal diagnostic accuracy compared to rigid thoracoscope due to their fully flexible bodies [7].

However, Gwin et al conducted a diagnostic pleuroscopy under local anaesthesia in nine patients using a gas sterilized flexible fibreoptic bronchoscope inserted through a 1 to 2 cm chest incision into the pleural space that suggested a high degree of diagnostic accuracy [16]. Pleuroscopy in one patient excluded the diagnosis of recurrent neoplasm on the pleural aspect of a bronchopleural fistula. Another patient had a pleuroscopic biopsy of the lung, which was the only method successful in diagnosing a metastatic renal carcinoma. The other seven patients were studied for pleural effusions which were undiagnosed after study of pleural fluid and/ or Abrams needle biopsy. In four of them, pleural implants of carcinoma were visualized and proved by biopsy. Three patients had negative pleuroscopy, two of these also being negative at subsequent thoracotomy. One was not explored because of extrathoracic metastases. The procedures were performed with minimal patient discomfort and no serious complications [16].

Yokoyama et al explored a technique for performing thoracoscopy under local anaesthesia using a 32 Fr chest tube and a flexible fibreoptic bronchoscope without a rigid thoracoscope for the diagnosis, inspection, and management of patients with pleurisy. Patients with pleural effusion who underwent thoracoscopy under local anaesthesia using a 32 Fr chest tube and a flexible fibreoptic bronchoscope were retrospectively studied. Thoracoscopy was safely performed using a 32 Fr chest tube and a flexible fibreoptic bronchoscope in the diagnosis and management of pleural effusion in all cases. The visualization of the pleura, diaphragm, and lung using this instrumentation was excellent in comparison to that normally obtained during surgical thoracoscopy. A forceps biopsy of the pleura or diaphragm could therefore be easily and effectively performed. The result of this study indicates that flexible bronchoscopy has clinical utility as a diagnostic tool for pleurisy; furthermore, this method is safe, effective and inexpensive, not only for surgeons but also for physicians [8].

A similar study conducted by Atta et al achieved successful histopathological diagnosis on all patients. The study revealed that 63 (75%) cases had malignant pathology and 21 (25%) cases had inflammatory pathology. Pleurodesis was performed and was successful in all the patients. Two (2.38%) patients developed empyema after the procedure, and they were successfully managed by intercostal tube drainage and antibiotic therapy. Other complications encountered included local wound infection in 3 (3.57%) cases, subcutaneous emphysema in 3 (3.57%) cases and chest pain following pleurodesis in 15 (17.85%) cases [17]. This study indicates that thoracoscopy using a flexible bronchoscope is equally safe and effective than traditional thoracoscopy and provides a good alternative technique.

Multiple trials compare the size, quality and diagnostic adequacy of biopsy specimens obtained at semi-rigid and rigid thoracoscopy. However, there are no head-to-head study comparing diagnostic yield between semi-rigid thoracoscopy and thoracoscopy using flexible bronchoscope. In a pilot study done by Rozman et al, the diagnostic accuracy was 100% for the rigid procedure and 97.6% for the semi-rigid procedure [18]. Dutt et al undertook a study to determine if pleuroscopy could be performed safely and with useful diagnostic yield using conscious sedation and introducing a flexible fiberoptic bronchoscope through a chest tube. They performed diagnostic pleuroscopy in patients whose pleural effusions remained undiagnosed after at least one diagnostic thoracocentesis. The overall diagnostic yield of this procedure was 97%. A confirmatory diagnosis was possible in 40 cases with the standard bronchoscope biopsy forceps (69%), 8 cases with a cryo forceps (14%) and in 10 cases with a double port technique (17%) [19] .

CHAPTER 4 RESEARCH METHODOLOGY

4.1 TYPE OF STUDY

This is a prospective, single-centre, open-label, two-arm parallel-group randomized controlled trial comparing disposable flexible bronchoscopy versus semi-rigid pleuroscopy among hospital patients with pleural effusion.

4.2 STUDY DESIGN

4.2.1 Period of Study

The study will recruit subjects from June 2026 to June 2028 (3 years).

4.2.2 Study Setting

The study will be conducted in the Endoscopy Centre , Hospital Canselor Tuanku Muhriz UKM (HCTM UKM).

4.2.3 Investigational Product and Comparator

Investigational Product

The investigational device evaluated in this study is the **UE Medical Single-Use Flexible Bronchoscope**, a sterile disposable flexible endoscope equipped with a 2.8-mm working channel. The device is designed to visualize the pleural cavity and permit pleural tissue sampling with standard biopsy forceps during medical thoracoscopy.

Comparator (Standard of Care)

The comparator device is the **Olympus LTF-260 Semi-Rigid Pleuroscope**, which represents the current standard-of-care instrument used for medical thoracoscopy at Hospital Canselor Tuanku Muhriz (HCTM) UKM. The semi-rigid pleuroscope features a flexible distal tip and a 2.8-mm working channel, enabling visualization of the pleural cavity and tissue acquisition during pleural biopsy.

Both devices are intended to achieve the same clinical objectives, namely pleural cavity inspection and pleural tissue sampling. The primary difference is that the investigational device is a single-use, disposable, flexible bronchoscope, whereas the comparator is a reusable, semi-rigid pleuroscope routinely used in clinical practice.

4.2.4 Sampling Population

This study will include all hospital patients with pleural effusion who undergo medical thoracoscopy (MT) using either a disposable flexible bronchoscope or a semi-rigid pleuroscope. Eligible patients will be randomly assigned in a 1:1 ratio using block randomization with a block size of two to ensure balanced allocation between the two study arms. In the event of technical difficulties or intraprocedural complications that preclude continuation with the allocated device, crossover to the alternative arm will be permitted at the discretion of the operator to ensure patient safety. All crossovers will be documented and analyzed accordingly. The study population will be explicitly recruited from patients admitted to the inpatient wards or referred to the specialized respiratory outpatient clinics of Hospital Canselor Tuanku Muhriz (HCTM) UKM, who require diagnostic intervention for unexplained pleural fluid accumulation.

Medical thoracoscopy is considered the standard of care for patients with undiagnosed exudative pleural effusion following non-diagnostic initial investigations. Participation in this study does not alter the indication for the procedure itself, but only determines the type of thoracoscopic device used during the procedure.

4.2.5 Inclusion Criteria

- Age ≥ 18 years
- Patient presents with an undifferentiated pleural effusion with or without initial diagnostic thoracocentesis, thereby necessitating definitive pleural tissue sampling.
- Demonstrated presence of a visually significant pleural effusion occupying at least one-third of the affected hemithorax on standard chest radiography, or a visually confirmed loculated effusion accessible via thoracic ultrasound mapping.
- The patient has demonstrated full willingness to participate and has signed the formal written informed consent form approved by the institutional review board.

4.2.6 Exclusion Criteria

- Age < 18 years
- Patients with contraindications to perform medical thoracoscopy, e.g.:
- Uncorrectable coagulopathy (e.g., platelet count <50,000/µL, INR >1.5 despite correction)
    - Severe hypoxemia not correctable with supplemental oxygen
    - Hemodynamic instability
    - Extensive pleural adhesions or obliterated pleural space on imaging
    - Uncontrolled cardiac arrhythmia or recent acute coronary syndrome
    - Severe pulmonary hypertension with high procedural risk
    - Inability to tolerate lateral decubitus position
    - Refusal to provide informed consent
    - Pregnancy
    - Previous ipsilateral pleurodesis or thoracic surgery significantly altering pleural anatomy

4.2.7 Study protocol

All patients referred for medical thoracoscopy who fulfil the study inclusion and exclusion criteria will be screened for eligibility. Eligible patients will be approached by the study investigators and provided with detailed information regarding the study. Written informed consent will be obtained prior to enrolment. The decision to perform medical thoracoscopy will be made independently by the treating respiratory specialist based on routine clinical indications and prior to study enrolment. Medical thoracoscopy represents the current standard of care for the investigation of undiagnosed pleural effusions after non-diagnostic conventional investigations. The research intervention is limited to the allocation of the thoracoscopic device used during the procedure and does not alter the patient's standard clinical management. The study intervention consists solely of allocation to either the investigational device (UE Medical Single-Use Flexible Bronchoscope) or the standard-of-care comparator device (Olympus Semi-Rigid Pleuroscope), while all other aspects of patient management remain unchanged.

Following consent, participants will be randomized in a 1:1 ratio using block randomization to either the Single-Use Flexible Bronchoscope Group or the Conventional Semi-Rigid Pleuroscope Group. Patients will not be allowed to choose their preferred intervention arm. Participants who decline the allocated intervention after randomization will be withdrawn from the study and managed according to standard clinical practice. Their withdrawal will be documented, and no further study-specific data will be collected.

All procedures will be performed at the Endoscopy Centre, Hospital Canselor Tuanku Muhriz (HCTM) UKM under local anaesthesia with conscious sedation according to institutional protocols. The procedures will be conducted by only one respiratory specialist experienced in pleural interventions, having independently performed more than fifty (50) medical thoracoscopy procedures. To ensure procedural consistency, standardization, and patient safety, other respiratory specialists will be available within the unit as observer during the procedure.

After establishment of pleural access and insertion of the trocar, the allocated videoscope will be introduced into the pleural cavity. A systematic examination of the pleural space will then be performed including inspection of the parietal pleura, visceral pleura, diaphragm, and accessible pleural surfaces. For it to be said to be adequate visualisation, all four layers of parietal pleura which are the costal, mediastinal, diaphramatic and cervical pleura must be seen according to standard reporting checklist. Any abnormal pleural lesions, nodules, thickening, adhesions, or suspicious areas will be identified and targeted for biopsy.

Procedure duration will be measured from the time the videoscope enters the pleural cavity through the trocar until complete removal of the videoscope from the trocar at the end of the procedure. This duration will be recorded in minutes for subsequent analysis.

Pleural biopsy specimens will be obtained using standard biopsy forceps through the working channel of the allocated device. To ensure uniformity of tissue sampling between both study arms, a minimum of ten (10) adequate pleural biopsy specimens will be obtained whenever technically feasible and clinically safe. An adequate pleural biopsy specimen is defined as a tissue sample deemed macroscopically satisfactory by the operator and suitable for histopathological assessment. Additional biopsies may be obtained at the discretion of the operator if clinically indicated.

In the event of technical difficulties, inadequate visualization, inability to obtain satisfactory tissue samples, equipment failure, or any circumstance that may compromise patient safety, crossover to the alternative device will be permitted at the discretion of the operator. The reason for crossover will be documented and included in the final analysis.

Upon completion of the procedure, a chest drain will be inserted according to standard institutional practice. Pleural fluid and biopsy specimens will be submitted for histopathological, microbiological, cytological, and other relevant investigations as clinically indicated. Patients will be monitored during the procedure and for at least 48 hours thereafter for any procedure-related complications.

Data collected will include demographic characteristics, procedural duration, procedural success, need for crossover, diagnostic yield, complications, and immediate post-procedural outcomes. All data will be recorded using standardized case report forms and entered into a secure study database for analysis.

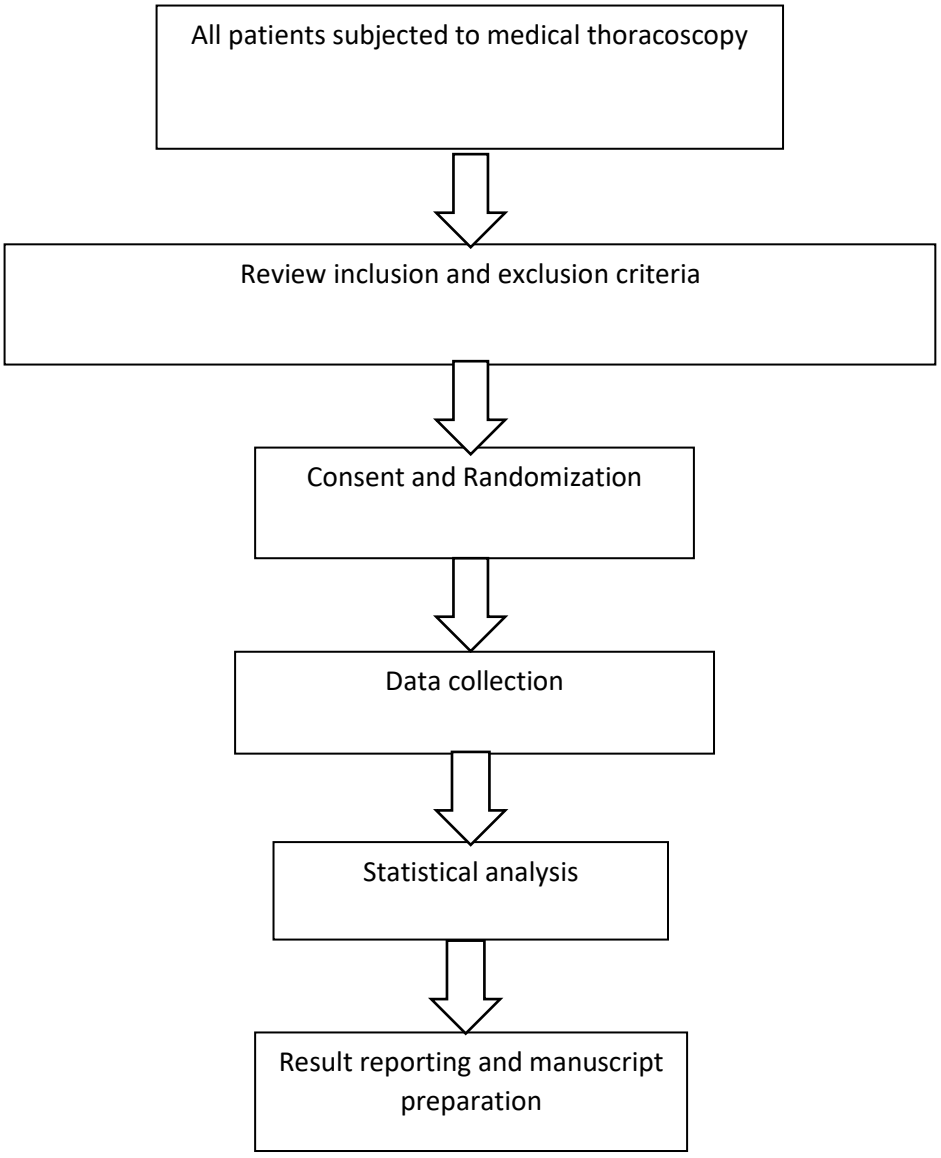
4.3 SAMPLE SIZE

The final target sample size for this pilot parallel-group study is 36 subjects in total, randomized in a 1:1 ratio into two comparative arms: the Flexible Single-Use Bronchoscopy Group (n=18) and the Conventional Semi-Rigid Pleuroscopy Group (n=18).

Because this is a Pilot Feasibility Randomized Controlled Trial (RCT), the sample size is not calculated to definitively prove non-inferiority or therapeutic superiority regarding clinical diagnostic yield or complication rates. Instead, the sample size of 18 subjects per arm is justified based on the Julious Method framework for pilot comparative trials. Julious establishes that a rule-of-thumb baseline of 12 evaluable subjects per group is statistically sufficient to capture precision, estimate the standard deviation of procedural parameters, and evaluate operational feasibility (such as recruitment rates and protocol compliance).

To safeguard the trial against an anticipated attrition, dropout, or technical baseline exclusion rate, the enrollment target was expanded by an additional 50% safety margin from 12 to a final robust cohort of 18 subjects per group. The variance data gathered from these 36 total comparative cases will provide the foundational statistical parameters required to accurately calculate the sample size for a subsequent, definitive multi-center clinical trial [20].

4.4 PATIENTS DATA COLLECTION PATHWAY



4.5 STATISTICAL ANALYSIS

All statistical analyses will be done using the Statistical Package for Social Sciences (SPSS) software version 28.

Descriptive Statistics

Descriptive statistics for Sociodemographic and Clinical Characteristics of Patients (frequencies and percentages) will be calculated. Differences across groups will be examined using the independent Student-t Test for continuous variables and Chi-Square test for categorical variables. A P value of less than 0.05 will be taken as statistically significant.

Bivariate Statistics

Differences between groups (Flexible Bronchoscope Group and Semi-Rigid Bronchoscope Group) with respect to Diagnostic Yield, Type of Complication, Rate of Complication, Size of Biopsy and Duration of Procedure will be analysed using the Independent Student-t test for continuous variables; for categorical variables, group differences will be examined by the Chi-square or Fisher exact tests as appropriate. In particular, the Fisher exact tests will be applied in case of an expected frequency of less than 5 in any cell in a 2x2 table. A p value of less than 0.05 will be considered as statistically significant.

Multivariate Statistics

To determine factors influencing the Diagnostic Yield (Dependent Variable), we will perform the Simple Logistic Regression (SLogReg) analysis initially and examining the statistical significance of each Independent Variable (Type of Bronchoscopy, Type of Complication, Rate of Complication, and Duration of Procedure) on the Dependent Variable (Diagnostic Yield). Then, we will perform the Multiple Logistic Regression (MLogReg) analysis including variables with a level of significance less or equal to 0.20 in the SLogReg and controlling for the effects of possible confounding variables (Age, Gender, BMI, Duration of procedure, Ethnicity, Amount of sedation, Presence of loculation and Co-Morbidity). A p value of less than 0.05 will be taken as the level of significance.

4.6 DUMMY TABLE

Table 1 Sociodemographic and Clinical Characteristics of Hospital Patients with Pleural Effusion

Variables	Flexible Group (n=75) No. (%)	Semi-rigid Group (n=75) No. (%)	P-value
Age (mean +/- SD)			
Gender			
Male			
Female			
Ethnicity			
Malay			
Chinese			
Indian			
Others (specify)			
Co-morbidities			
Diabetes Mellitus			
Hypertension			
Ischaemic heart Disease			
Heart Failure			
Previous stroke			
Dyslipidaemia			
Others			
Pleural fluid investigations			
Total leukocyte count (cells/uL)			
Protein (g/dL)			
Glucose (mmol/L)			
Adenosine deaminase (units/L)			
Presence of loculations			
Chest radiograph			
Chest CT scan			
Thoracic ultrasound			
By any technique			
BMI (kg/m^2)			
Duration of bronchoscopy (min)			
Sedation given			
Midazolam			
Fentanyl			

Table 2 Diagnostic Yield, Complication Type and Rate, Biopsy Size and Duration of Procedure using Single Use Flexible Bronchoscopy versus Semi-Rigid Pleuroscopy in Hospital Patients with Pleural Effusion

Variables	Flexible Group (n=18) No. (%)	Semi-rigid Group (n=18) No. (%)	Test*	P-value
Diagnostic Yield				
Complication				
• Type				
• Rate (no./procedure)				
Biopsy Size (mm)				
Duration of Procedure (min)				

* Independent Student-t test for continuous variables; Chi-Square test for categorical variables

Table 3 Predictors of Diagnostic Yield Using Single-Use Bronchoscopy in Hospital Patients with Pleural Effusion

(Multiple Logistic Regression Analysis)

CHAPTER 5 OPERATIONAL TERM DEFINITION

5.1 MEDICAL THORACOSCOPY

MT/pleuroscopy is a minimally invasive procedure that allows access to the pleural space using a combination of viewing and working instruments. This method allows for basic diagnostic (undiagnosed pleural fluid or pleural thickening) and therapeutic procedures (pleurodesis) to be safely performed. It requires one-lung ventilation for adequate creation of working space in the hemithorax. MT has the ability to provide complete visualization of the entire hemithorax, thus allowing multiple angles of attack to the pleural, pulmonary (parenchymal), and mediastinal pathology. It also enables the introduction of multiple instruments into the operative field to allow for both basic and advanced procedures to be performed safely [21].

5.2 FLEXIBLE SINGLE-USE BRONCHOSCOPE

The investigational product used in this study is the UE Medical Single-Use Flexible Bronchoscope. This disposable flexible endoscope is being evaluated as an alternative platform for performing medical thoracoscopy and pleural biopsy. The flexible bronchoscope is a solid instrument composed of thousands of glass fibres that transmit light for illumination and imaging. The tip of the instrument can be deflected to guide it into the desired path or location. Majority of flexible bronchoscopes have a small suction channel through which secretions may be aspirated, fluids may be delivered to the airways, or small flexible instruments may be passed. Instruments, ranging from 4.2 to 6.3 mm in diameter, are used in adults. These instruments have suction channels ranging from 2.0 to 3.2 mm in diameter [22]. We are using the UE Medical disposable bronchoscopy , with an instrument channel of 2.8 mm.

5.3 SEMI-RIGID PLEUROSCOPE

Similar to a rigid pleuroscope, the proximal portion (handle and shaft) is stiff, while similar to a flexible bronchoscope, the distal end is smaller in diameter and flexible so that the tip can be flexed or extended two-dimensionally. Similar to a flexible bronchoscope, the handle, suction, and a working channel can accommodate accessories such as a biopsy forceps. In addition, the semi-rigid endoscope is compatible with flexible bronchoscopy light sources and video processors, thereby, allowing this instrument to be readily adapted for use in the endoscopy suite.

In general, comparable diagnostic results and safety profiles have been reported between rigid and semi-rigid thoracoscopy, but similar to flexible equipment, adhesions or loculations may impact negatively on the success of semi-rigid thoracoscopy [23]. We are using the semi-rigid LTF-E 260 scope with a 2.8 mm diameter working channel, produced by Olympus, Tokyo, Japan.



5.4 DIAGNOSTIC YIELD

Diagnostic yield is defined as conclusive diagnosis derived from any sample taken during MT in corelation to other investigation to support diagnosis.

5.5 COMPLICATION TYPE

Complication type is defined as the type of complication during and after each procedure that are directly related to the procedure itself.

5.6 COMPLICATION RATE

Complication rate is defined as the number patients with complications during and after each procedure that are directly related to the procedure itself measured against the total number of patients undergoing each procedure.

5.7 DURATION OF PROCEDURE

Duration of procedure is defined as the duration from the point videoscope inserted into the pleural cavity until the video scope were removed upon completion of procedure.

CHAPTER 6 GANTT CHART

Progression / Timeline	**Mac-Jun 2026**	**June 2026**	**September 2026-January 2028**	**Jan 2028-Mac 2028**	**April 2028**	**May 2028**	**June 2028**
Formulation of Proposal							
Submission of Proposal to Research & Ethics Committee							
Data Collection							
Data Entry and Analysis							
Preliminary Data Presentation							
Project Report Presentation							
Final Project Report Submission							

CHAPTER 8 RESEARCH INFORMATION
INFORMATION SHEET FOR PATIENTS

Research Title:
A Pilot Randomized Controlled Trial Comparing Safety and Feasibility of Medical Thoracoscopy using Single-use Flexible Bronchoscope versus Semi-Rigid Pleuroscope among Hospitalized Patients with Pleural Effusion (FLEXPLEUR2)

Researchers:
Prof. Dr Mohamed Faisal Abdul Hamid
Dr Mas Fazlin Mohamad Jailaini
Dr Haji Azat Azrai Dato Azmel
Dr Manmeet Singh A/L Manjit Singh

Place of Study: Endoscopy Centre, Respiratory Unit, Hospital Canselor Tuanku Muhriz (HCTM), UKM.

Introduction
"Fluid around the lungs" is a common problem where extra fluid builds up in the small space surrounding your lungs. When regular medical tests cannot find the reason for this fluid, doctors perform a procedure called medical thoracoscopy to look into this space and take tiny tissue samples (biopsies) for testing. To do this, the doctor makes a small cut in the skin of your chest wall and inserts a tiny camera.
Medical thoracoscopy is an established standard-of-care procedure used when routine investigations fail to identify the cause of pleural effusion. At HCTM UKM, this procedure is routinely performed using a semi-rigid pleuroscope. In this study, we are evaluating whether a single-use flexible bronchoscope can be used as an alternative device to perform the same procedure safely and effectively.This study aims to see if the flexible camera works just as well, is just as safe, and takes the same amount of time as the standard camera**.**

Purpose of the Study
The goals of this study are:

- To see if both types of cameras are equally successful in finding the true cause of the fluid build-up.
- To compare the safety and types of side effects or complications that might happen within 2 days (48 hours) after the procedure.
- To see if one camera is faster to use than the other.

Study Procedures
If you agree to take part in this study:

- You have already been identified by your treating respiratory specialist as requiring medical thoracoscopy as part of your routine medical care. Participation in this study does not change the decision to perform medical thoracoscopy. The study only determines which device will be used to perform the procedure.
- You will be assigned to one of two study groups completely by chance (similar to flipping a coin). Neither you nor your doctor will be able to choose which study device will be used.
    - Group 1: The doctor will use the new, single-use flexible camera.
    - Group 2: The doctor will use the standard, partially stiff camera.

If you do not wish to proceed with the device allocated to you, you may withdraw from the study at any time. Your withdrawal will not affect your medical care, and your treating physician will continue to manage you according to standard clinical practice.

- The procedure will be done using numbing medicine (local anesthesia) on your chest skin along with relaxing medicine (sedation) to keep you comfortable, which is exactly how the hospital normally does it.
- The medical team will closely monitor you for any side effects or discomfort during the procedure and up to 48 hours afterward.

Please Note: If the doctor runs into any technical difficulties or has any safety concerns during the procedure, they can switch cameras immediately to ensure your safety.

Benefits

There may be no direct, immediate benefit to your health from taking part in this study. However:

- Your choice to participate can help us improve future medical tools used to find the causes of chest fluid build-up.
- This study could help find an easier-to-get and more affordable way to diagnose chest and lung conditions for future patients.

Risks

Looking into the chest space with a camera is a standard, routine procedure. Possible risks and side effects include:

- Pain or discomfort where the cut is made
- Minor bleeding
- Infection
- Air leak (air getting trapped outside the lung)
- Air bubbles under the skin (feels like bubble wrap when pressed)
- Mild fever
- On very rare occasions, minor lung injury or a brief struggle to breathe comfortably

All procedures will be carried out by highly experienced lung specialists, and our team will follow strict, standard safety rules at all times.

Voluntary Participation

Taking part in this study is 100% your choice. You have the right to say no, or to change your mind and leave the study at any time. Choosing not to participate will not change, delay, or hurt your regular medical care at this hospital in any way.

If you decide not to participate in this study, or if you withdraw after enrolment, you will still undergo the necessary investigations and treatment recommended by your treating physician. Your medical care will not be affected in any way.

Choosing not to participate will not change, delay, or adversely affect your regular medical care at this hospital in any way.

Confidentiality

All of your personal and medical details will be kept completely private. Only our direct research team and the hospital's Ethics Review Board will be allowed to look at your study records. Your name, ID number, and face will never be shared or shown in any medical reports or shared papers.

Study Costs and Payment

- **Research Costs:** There are absolutely no extra or hidden out-of-pocket costs to you for joining this study. The cost of the single-use camera equipment is completely paid for by the study's research fund.
- **Hospital Bills:** You will still be responsible for paying your regular, standard hospital admission bill, routine lab tests, and normal procedure fees exactly as you would for regular hospital care at HCTM UKM.
- **Payment:** You will not receive any money, cash rewards, or payments for volunteering your time to participate in this trial

Contact Information

If you have questions regarding this study, please contact:

Prof. Dr Mohamed Faisal Abdul Hamid
Respiratory Unit, Department of Internal Medicine
Hospital Canselor Tuanku Muhriz, UKM

CHAPTER 9

INFORMED CONSENT FORM

A Pilot Randomized Controlled Trial Comparing Safety and Feasibility of Medical Thoracoscopy using Single-use Flexible Bronchoscope versus Semi-Rigid Pleuroscope among Hospitalized Patients with Pleural Effusion (FLEXPLEUR2)

I …… I/C NO: …….....

I have read and understood the 'Patient Information Sheet' attached to this 'Patient Consent Form'. Information regarding the reasons for the study, how it will be carried out and the inconveniences that are expected has been explained to me. I have been allowed to ask questions about this study and these questions have been answered to my satisfaction.

I understand that my participation in this study is voluntary and I can withdraw myself from this study at any point of time during the test. My treatment will be continued and will not be affected by my decision to not participate in this study.

I hereby allow the collected information to be analysed in the computer and the information to be forwarded to the medical authorities, if necessary. I hereby consent to participate in this study

……..
Signature / Thumbprint of patient
Name : …….
IC No : …….
Date : …….

.....

Signature / Thumbprint of witness
Name : ……....
IC No : …….....
Date : .....

.....

Signature of Doctor
Name : ……
IC No : ……
Date : .....

CHAPTER 10 APPENDICES

APPENDIX A
DATA COLLECTION SHEET

Patient's Sticker

Name: ……
Contact Number: …….
Age: ……
Gender: ……
Ethnicity: …….
Background Medical Problem:

- Diabetes Mellitus ☐
- Hypertension ☐
- Ischaemic heart Disease ☐
- Heart Failure ☐
- Previous stroke ☐
- Dyslipidaemia ☐
- Others: …….

Weight (kg): ……. Height (m): …… BMI (kgm^{-2}): ……

Indication For Flexible Bronchoscopy:

1. **_____**
2. **_____**

Sedation given:

IV Midazolam ☐ **mg +** ☐ **mg**

IV Fentanyl ☐ **mg +** ☐ **mg**

Patient is in which group?

Flexible bronchoscopy ☐ **Semi-rigid pleuroscopy** ☐

If plural fluid taken, what was it sent for:

CNS ☐

AFB ☐

TB CNS ☐

TB PCR ☐

TB Gene Expert ☐

Cytology ☐

Cell Count ☐

Gram Stain ☐

Others: _____ ☐

If Biopsy was taken, where was it taken from:

_____

If Biopsy taken, what was it sent for

HPE ☐

CNS ☐

Others: _____ ☐

Duration of thoracoscopy: _____ Hr_____ mins

CT imaging

Pleural thickness (cm):

Diagnostic outcomes of MT:

Tuberculosis ☐

Nonspecific inflammation ☐

Sarcoidosis ☐

Aspergilosis ☐

Rheumatoid nodule ☐

Malignant ☐

Undiagnosed ☐

Complications of MT:

Major complications

- **Mortality** ☐
- **Lung laceration** ☐
- **Bleeding** ☐
- **Re-expansion pulmonary oedema** ☐
- **Prolonged air leak** ☐
- **Mediastinal emphysema** ☐

Minor complications

- **Subcutaneous emphysema** ☐
- **Pain** ☐
- **Fever** ☐
- **Cutaneous infection in entry site** ☐

CHAPTER 8 REFERENCES

1. Rahman, N.M., et al., *Local anaesthetic thoracoscopy: British Thoracic Society Pleural Disease Guideline 2010.* Thorax, 2010. **65 Suppl 2**: p. ii54-60.
2. Maskell, N.A., R.J. Butland, and S.o.C.C.B.T.S. Pleural Diseases Group, *BTS guidelines for the investigation of a unilateral pleural effusion in adults.* Thorax, 2003. **58 Suppl 2**(Suppl 2): p. ii8-17.
3. Loddenkemper, R., et al., *Medical thoracoscopy/pleuroscopy: step by step.* Breathe, 2011. **8**(2): p. 156-167.
4. Collins, T.R. and S.A. Sahn, *Thoracocentesis. Clinical value, complications, technical problems, and patient experience.* Chest, 1987. **91**(6): p. 817-22.
5. Valsecchi, A., S. Arondi, and G. Marchetti, *Medical thoracoscopy: Analysis on diagnostic yield through 30 years of experience.* Ann Thorac Med, 2016. **11**(3): p. 177-82.
6. Fielding, D., P. Hopkins, and D. Serisier, *Frozen section of pleural biopsies at medical thoracoscopy assists in correctly identifying benign disease.* Respirology, 2005. **10**(5): p. 636-42.
7. Davidson, A.C., et al., *Thoracoscopy: assessment of a physician service and comparison of a flexible bronchoscope used as a thoracoscope with a rigid thoracoscope.* Thorax, 1988. **43**(4): p. 327-332.
8. Yokoyama, T., et al., *Medical Thoracoscopy Performed Using a Flexible Bronchoscope Inserted through a Chest Tube under Local Anesthesia.* Diagn Ther Endosc, 2009. **2009**: p. 394817.
9. Menzies, R. and M. Charbonneau, *Thoracoscopy for the diagnosis of pleural disease.* Ann Intern Med, 1991. **114**(4): p. 271-6.
10. Boutin, C., P. Cargnino, and J.R. Viallat, *Thoracoscopy in the early diagnosis of malignant pleural effusions.* Endoscopy, 1980. **12**(4): p. 155-60.
11. Loddenkemper, R. and C. Boutin, *Thoracoscopy: present diagnostic and therapeutic indications.* Eur Respir J, 1993. **6**(10): p. 1544-55.
12. Manoharan, A. and C. Argáez, *CADTH Rapid Response Reports*, in *Pleuroscopy for the Diagnosis of Cancer in Patients with Pleural Effusion: A Review of the Diagnostic Accuracy, Safety, Cost-Effectiveness and Guidelines*. 2020, Canadian Agency for Drugs and Technologies in Health Copyright © 2020 Canadian Agency for Drugs and Technologies in Health.: Ottawa (ON).
13. Shamsuddin, A.R., et al., *Comparison of diagnostic yield and complication of medical thoracoscopy using Flexible Bronchoscope versus Semi-Rigid Pleuroscope among Hospitalized Patients with Pleural Effusion (FLEXPLEUR): a retrospective observational study.* Journal of Thoracic Disease, 2025. **17**(6): p. 3631-3642.
14. Marchetti, G.P., V. Pinelli, and G.F. Tassi, *100 years of thoracoscopy: historical notes.* Respiration, 2011. **82**(2): p. 187-92.
15. Senno, A., et al., *Thoracoscopy with the fiberoptic bronchoscope.* The Journal of Thoracic and Cardiovascular Surgery, 1974. **67**(4): p. 606-611.
16. Gwin, E., et al., *Pleuroscopy and pleural biopsy with the flexible fiberoptic bronchoscope.* Chest, 1975. **67**(5): p. 527-31.
17. Atta, M.A., et al., *Fiberoptic thoracoscopy in management of exudative pleural effusion.* Egyptian Journal of Chest Diseases and Tuberculosis, 2012. **61**(4): p. 405-411.
18. Rozman, A., et al., *Rigid versus semi-rigid thoracoscopy for the diagnosis of pleural disease: a randomized pilot study.* Respirology, 2013. **18**(4): p. 704-10.
19. Tiyas Sen Dutt, S.Z.T., B.V. Murali Mohan, *Diagnostic and Therapeutic Pleuroscopy Using a Flexible Fiberoptic Bronchoscope for Resource-poor Environments: A Case Series.* Indian J Chest Dis Allied Sci, 2017. **4**(59): p. 173-176.

20. Julious, S.A., *Sample size of 12 per group rule of thumb for a pilot study.* Pharmaceutical Statistics: The Journal of Applied Statistics in the Pharmaceutical Industry, 2005. **4**(4): p. 287-291.
21. *Medical Thoracoscopy/Pleuroscopy*. 2003: CHEST - Journal. p. 1712-1713.
22. *Flexible Bronchoscopy*. 2003: CHEST - Journal. p. 1694-1695.
23. Shaheen, M.M.A.M., et al., *The diagnostic role of thoracoscope in undiagnosed pleural effusion: Rigid versus flexible.* Egyptian Journal of Chest Diseases and Tuberculosis, 2014. **63**(3): p. 635-642.