Study Title: STREAMLINE: Smarter Therapeutic and Diagnostic Intervention in Malignant Pleural Effusion: Feasibility Study

Internal Reference Number / Short title: STREAMLINE

Ethics Ref: Insert

IRAS Project ID: 328727

ISRCTN Ref:

Date and Version No: 1.0 03 Aug 2023

Chief Investigator:
Professor Najib M Rahman
Professor of Respiratory Medicine and Consultant
Director, Oxford Respiratory Trials Unit
Churchill Hospital
Old Road
Headington
Oxford, OX3 7LE
E-mail: Najib.rahman@ndm.ox.ac.uk

Investigators:
Dr Dinesh Addala
Oxford Centre for Respiratory Medicine
Churchill Hospital
Old Road
Headington
Oxford, OX3 7LE
E-mail: dinesh.addala@ouh.nhs.uk

Sponsor: University of Oxford

Funder: NIHR Doctoral Research Fellowship (Dinesh Addala)

Chief Investigator Signature: The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol

Statistician Signature:

No potential conflicts of interest

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

Trial Title: STREAMLINE: Smarter Therapeutic and Diagnostic Intervention in Malignant Pleural Effusion: Feasibility Study
Protocol Date and Version No: V1.0 03 Aug 2023

Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	**Signature**	**Site name or ID number**	**Date**

Following any amendments to the protocol, this page must be updated with the new protocol version number and date and re-signed by the site PI.

TABLE OF CONTENTS

1. KEY CONTACTS

Insert full details of the key trial contacts including the following; please add/remove headings as necessary.

Chief Investigator	Professor Najib M Rahman Professor of Respiratory Medicine and Consultant Oxford Centre for Respiratory Medicine Director, Oxford Respiratory Trials Unit Churchill Hospital Old Road Headington Oxford, OX3 7LE
Sponsor	University of Oxford Research Governance, Ethics and Assurance Team 1st floor, Boundary Brook House Churchill Drive Headington Oxford OX3 7LQ RGEA.Sponsor@admin.ox.ac.uk Tel: 01865 616480
Funder(s)	NIHR Doctoral Research Fellowship Grant
Clinical Trials Unit	Oxford Respiratory Trials Unit CCVTM, Churchill Hospital Headington Oxford, OX3 7LE Tel: 01865 225205 ORTU@ndm.ox.ac.uk
Committees	Study Management Group Study Steering committee

2. LAY SUMMARY

A malignant pleural effusion (MPE) is a buildup of fluid around the lungs due to any type of cancer that has either started or spread to the lining of the lungs (pleura). This is a very common problem, effecting over 100 people per day in the UK. Typically, people with MPE experience debilitating breathlessness due to fluid buildup. Another challenge for people suffering with MPE is the challenge to reach a diagnosis which can delay treatment with, for example chemotherapy.

At present, in the standard investigation and management pathway for patients with a pleural effusion suspected to be due to cancer, patients have some fluid drawn off and the cells analysed for the presence of cancer cells. This often is not successful and recent data from our site has suggested only 20% of patients receive enough information from fluid alone to treat their cancer. The patient therefore has to come back for a biopsy of the lining of the lung. Once a diagnosis is secured, steps to stop the fluid around the lungs coming back are taken, one of which is to insert a long-term tube in the chest (indwelling pleural catheter, IPC) which is dressed and can be used a few times per week to let fluid out (done by a district nurse or carer at home). Typically, with the current pathway, patients wait 6 weeks for a diagnosis and over 2 months for long term control of breathlessness. Many of these patients have a life expectancy of 3-12 months and as such a large proportion of this is spent breathless and without a diagnosis.

We aim to create a new accelerated pathway (diagnosing and managing fluid build up, which is all part of standard care) for patients suffering with potential MPE, such that at their first visit, patients will be offered a biopsy which give them the highest likelihood (80-95% success rate), of reaching a diagnosis and in the same (first) visit, the patients will have a long term chest tube fitted (indwelling pleural catheter, IPC) so they are not left breathless and needing multiple procedures. This could achieve diagnosis and treatment in one procedure rather than multiple separate procedures in the standard pathway.

Our study will randomise patients in to either a group having the current standard care pathway, or into the accelerated pathway. We will assess key parameters such as the time to diagnosis, overall duration of breathlessness while awaiting a diagnosis, and quality of life.

If randomised to the accelerated pathway, a more extensive first visit (pleural biopsy and IPC) will be planned, compared to the standard care pathway and as such a small-scale trial of 40 patients is required to assess whether patients find this acceptable and this is deliverable within the NHS.

3. SYNOPSIS

Study Title	Smarter Therapeutic and Diagnostic Intervention in Malignant Pleural Effusion: Feasibility Study		
Internal ref. no. / short title	STREAMLINE		
Sponsor	University of Oxford Research Governance, Ethics and Assurance Team 1st Floor, Boundary Brook House Churchill Drive Headington Oxford OX3 7LQ		
Funder	NIHR		
Study Design	Prospective randomised feasibility study		
Study Participants	Patients with first presentation of probable malignant pleural effusion (MPE)		
Sample Size	40		
Planned Study Period	27 months (3 month set up, 18-month recruitment, 3 month follow up and 3 month close out)		
Planned Recruitment period	2 October 2023 – 2 January 2026		
	Objectives	Outcome Measures	Timepoint(s)
Primary	Feasibility of recruitment and data collection.	40 patients randomised 1:1 between standard pathway for MPE and accelerated pathway. proportion of eligible patients who agree to randomisation / data completeness / availability and participant completion	At recruitment completion

Secondary	1. Mean change and standard deviation in breathlessness	1. 100mm VAS scores completed before and after the first procedure and weekly thereafter	3 times per week for 6 weeks from randomisation
	2. Patient anxiety and depression	2. Hospital anxiety and depression score (HADS);	Weekly over six weeks from randomisation
	3. Health Related Quality of Life	3. QLQ-C30 and EQ 5D 5L questionnaire	Weekly over six weeks from randomisation
	4. Time to actionable histopathology/diagnosis	4. Cancer multi-disciplinary team consensus	Four weeks post intervention
	5. Healthcare utilisation	5. Number of pleural procedures and days in hospital post enrolment	End of recruitment
	6. Assess the acceptability to patients and patient priorities	6. Perform structured qualitative interviews with a proportion of patients in both the standard care arm, accelerated arm and those declining participation	Until end of recruitment
Patient Group	Patients with suspected malignant pleural effusion, based on any of: clinical presentation, imaging, prior asbestos exposure or history of malignancy:		
Intervention(s)	First procedure as a pleural biopsy (local anaesthetic thoracoscopy if available or image guided biopsy if local constraints preclude thoracoscopy) AND Indwelling pleural catheter (IPC) insertion in a single procedure = the accelerated pathway		
Comparator	Standard care pathway as defined by the current British Thoracic Society Guidelines (2010 and updated version 2022), with first procedure as pleural aspiration only, followed by subsequent procedures for tissue biopsy and definitive fluid control as required.		

4. ABBREVIATIONS AND GLOSSARY

AE	Adverse event
CI	Chief Investigator
CRF	Case Report Form
CRP	C-reactive Protein
CT	Computerised Tomography Scan
MPE	Malignant Pleural Effusion
IPC	Indwelling Pleural Catheter
LAT	Local Anaesthetic Thoracoscopy
VAS	Visual Analogue Scale
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
EORTC	European Organisation for Research and Treatment of Cancer
HADS	Hospital Anxiety and Depression Scale
QLQ-C30	Core Quality of Life Questionnaire
NHS	National Health Service
ORTU	Oxford Respiratory Trials Unit
PI	Principal Investigator
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGEA	Research Governance, Ethics and Assurance Team
SAE	Serious Adverse Event
TPA	Tissue Plasminogen Activator
TSC	Trial Steering Committee
SOP	Standard Operating Procedure
VATS	Video Assisted Thoracic Surgery
Standard Pathway	The current, standard investigation and management pathway for patients with suspected malignant pleural effusion. This begins with pleural aspiration as the first procedure.
Accelerated Pathway	The intervention arm of the study. This pathway involves undertaking a pleural biopsy and indwelling pleural catheter as the **first procedure for investigation and management of a pleural effusion suspected to be due to cancer**

5. BACKGROUND AND RATIONALE

Background

Malignant pleural effusion (MPE) is the build-up of fluid between the lung and the chest wall as a result of cancer cells in the pleura. MPE is a common complication of cancer, with an incidence of 50 000 per year in the UK[1] and occurs in up to 15% of people with cancer. MPE can be associated with any type of cancer, both primary pleural malignancy (mesothelioma) and the result of secondary spread from other sites including lung, breast and ovarian[2]. The effects upon patients living with MPE are profound, with significant breathlessness, fatigue and impact on daily activity[3].

What is currently done for a patient with suspected MPE?

The current investigation and management pathway for a new pleural effusion in the UK and Europe is 11 years old and does not account for recent data. The current BTS MPE guidelines which are in public consultation currently still suggest the same diagnostic pathway in almost all cases, as specified below.

The pathway begins with a symptomatic patient presenting to either primary or secondary care with breathlessness, and basic imaging (chest radiograph) demonstrating a unilateral pleural effusion. The priorities for the patient and clinicians are to 1) establish a diagnosis while also 2) providing relief of symptoms. The initial procedure involves aspiration of pleural fluid with around 50mls sent for laboratory diagnostic analysis and assessment of cytology to establish a malignant diagnosis. In addition, a further 1-1.5 litres of fluid may be withdrawn to improve breathlessness.

However, recent evidence suggests that the initial pleural aspiration may not be helpful. The sensitivity of pleural fluid alone is low; even when malignant cells are detected, the sample is insufficient to provide information on required oncological treatment (actionable cytology), and the fluid recurs in the majority of patients. Following this first procedure, the patient therefore requires further procedures to achieve a diagnosis (biopsy of the pleura), and a further ‘definitive’ pleural fluid control procedure. This is conducted using either talc pleurodesis (which cannot be conducted before final diagnosis as it ‘seals’ the pleural space preventing further biopsy) or indwelling pleural catheter insertion (IPC) to control breathlessness and prevent re-admission to hospital. Further biopsies can be undertaken after IPC insertion.

Pilot work has demonstrated that the total duration of this pathway is long. Patients experience significant breathlessness between repeated procedures, and there is an average of 30 days to diagnosis and 70 days to definitive pleural fluid and breathlessness control. Leveraging the modern data, this suggests that a new and accelerated pathway should be considered for both a quicker diagnosis, and better symptom control from the patient perspective.

The Patient Perspective

Published work in this area has ignored the vital patient perspective in terms of priorities of diagnosis and symptom management. Pleural aspiration does not prevent fluid recurrence and further

breathlessness; approximately 30% of patients will experience fluid recurrence within two weeks following aspiration and this increases over time[4].

Patients thus often undergo multiple procedures for symptoms, while waiting for final diagnostics and definitive management. Patients experience significant uncertainty and anxiety within this pathway[5]. Pilot PPI data (n=17) demonstrates 84% of patients with MPE had undergone 2 or more procedures prior to indwelling catheter insertion and 65% had been breathless for over one month, with 60% having to make an emergency call for fluid drainage or admission to hospital. The ~70 day pathway length is similar in other pleural centres (Bristol, Glasgow) and likely longer in non-specialist units. This duration forms an unacceptable proportion of the 3-12 month total survival in patients with MPE.

Summary: The current MPE pathway results in prolonged breathlessness and long delays to an 'actionable diagnosis' (i.e. information that can guide systemic cancer treatment).

Benefits to patients and addition to current research

The proposed study seeks to target the delay to diagnosis and prolonged breathlessness by combining a definitive diagnostic procedure (pleural biopsy) and fluid management (IPC) as the **first intervention.** This will achieve an earlier diagnosis, fluid control, and control of breathlessness as early as possible in the diagnostic pathway. The novel pathway has the potential to provide months of additional symptom benefit, reduce time to diagnosis, prevent multiple repeat procedures and reduce costs.

Work from our unit and others has shown the unacceptable diagnostic delays, prolonged breathlessness and repeated procedures in patients with MPE[6].

Randomised trials to date in MPE have compared definitive treatments, e.g. talc pleurodesis with indwelling pleural catheter[7] [8]. However, these interventions were implemented **after the initial diagnostic pathway** and **do not capture** the need for multiple procedures leading up to this point, or the frequent breathlessness patients experience until definitive fluid management.

Great progress has been made in other areas of care (e.g. lung cancer) to speed up diagnostics (target 14 days) and treatment, with current guidelines advocating early CT scanning, and a 'direct to biopsy' approach[9]. We aim with this research to bring the much slower MPE pathway in line with similar rapid cancer pathways.

Why do we need a clinical study to demonstrate feasibility and patient benefit?

High quality evidence is required to demonstrate that the new pathway is acceptable to patients and provides demonstrable positive impact on quality of life. The proposed STREAMLINE pathway includes invasive interventions such as pleural biopsy and indwelling pleural catheter insertion as a first procedure. This represents significant impact on patients' day to day life and it is essential to capture the potential benefits to breathlessness and time to diagnosis versus the potential psychological and physical impact of a long term pleural catheter and a more invasive first procedure. There is a risk of a small number of patients receiving a therapeutic intervention targeted to malignant pleural effusion that receive a final diagnosis that is not cancer.

Benefits to healthcare

UK data has shown that IPCs are more cost effective than talc pleurodesis[10] in the definitive management of MPE in patients with <14 weeks survival. Other studies have shown that inpatient management of pleural effusion can cost up to seven times that of outpatient management[11]. In addition, these studies were conducted prior to the COVID-19 pandemic, and in our semi-structured interviews with patients on the MPE pathway, the majority were keen to avoid inpatient admission and the associated risks. The benefit of avoiding emergency admission (a common occurrence within the current MPE pathway) cannot be understated in terms of healthcare costs. Finally, earlier control of pleural fluid has the potential to maintain patient's performance status and allow treatment with chemotherapy.

Summary: A streamlined diagnostic and therapeutic pathway has the potential to reduce total breathlessness for patients, improved time to actionable diagnosis and reduce admissions. If feasible, this study will provide key parameters (primary outcome, recruitment rate, sample size) to conduct a definitive larger trial which could change the paradigm for MPE management in thousands of patients per year.

Review of existing evidence

Diagnostic Modalities

The diagnostic sensitivity of pleural fluid cytology is poor at only 37- 43%[12] in MPE, and even less in mesothelioma (6%). In addition, it is now clear that the finding of malignant cells in fluid alone is often insufficient to guide oncological treatment[13], due to the increase in personalised oncological therapy requiring molecular markers to guide chemotherapy and immune mediated treatments[14 15]. *Even in patients with positive cytology*, >65% require a subsequent biopsy to guide initial oncological treatment. *Thus, pleural fluid alone is rarely sufficient to make a diagnosis.*

Ultrasound and CT guided pleural biopsies have a similar diagnostic yield, providing adequate tissue for diagnosis in >95% of patients and actionable histo-cytology in a very high proportion. However, ultrasound guided biopsies are faster to undertake, can be conducted by physicians at the first meeting with the patient without putting on a CT waiting list, cost less and do not expose patients to ionizing radiation[16] . Ultrasound guided biopsies can be performed by physicians and can be easily combined with therapeutic drainage procedures such as IPC. CT guided biopsies require radiologists and CT scan time, and are generally not combined with definitive fluid drainage.

Thoracoscopic biopsies are the preferred method of diagnosis for mesothelioma[3 17], as direct visual inspection of the pleura is possible, and larger biopsies are possible which are necessary for diagnosis. Thoracoscopy can be performed under local anaesthetic and combined with IPC insertion as a daycase procedure.

Therapeutic Modalities

Once a diagnosis of MPE is established, there are several treatment options for fluid control. The historical method of definitive fluid control has been to insert a chest drain, admit to hospital and when fluid has been completely drained, instill talc slurry via the chest tube (talc pleurodesis). This has an approximately 30% failure rate, and necessitates an inpatient hospital stay of between 3-5 days[18].

Indwelling pleural catheters (IPCs) are long term drains which are inserted as day case procedures, do not require admission to hospital and can be retained indefinitely. Pleural fluid control is then undertaken by periodic drainage at the patient's own home by either a family member or district nurse and can be adjusted to meet the patient's requirements. IPCs improve symptoms in 96%[19] and have been used as a treatment option in the NHS for many years.

Patients treated with IPCs can achieve auto-pleurodesis (i.e. the fluid stops being produced) with regular drainage in between 24-47% of cases. When this occurs, IPC removal is undertaken with local anesthetic in a single outpatient visit.

For this study, the hypothesis is that early IPC insertion (i.e. at the time of initial biopsy) will provide more immediate and longer-term control of breathlessness in contrast to their use late in the current pathway. With earlier use, this may prevent the current variability in breathlessness experienced by patients who require repeat procedures.

Recent large scale trials in MPE management with IPCs

The two largest randomised control trials in MPE (TIME2[7], AMPLE[8]) illustrate that IPCs are an effective method of definitive pleural fluid control compared to talc pleurodesis, when both are used at the end of the diagnostic pathway (after diagnosis is secured). IPCs reduced hospital stay vs talc slurry and reduced the need for further pleural procedures. Breathlessness at 30 or 42 days post intervention was not significantly different between IPC and talc groups.

Prospective studies[20] [21] have shown that talc slurry via the IPC or aggressive (daily) drainage of IPCs can increase pleurodesis rates from <25% to up to 47%.

No trial to date has combined an early biopsy strategy with definitive fluid control via IPC insertion, which this study seeks to achieve. In the planned patient population, talc pleurodesis as a 'first' intervention is not an option, as this would 'seal' the pleural space in 70% of cases, making any further diagnostics such as repeat biopsy attempts almost impossible. In contrast, with IPCs, further biopsies after insertion are possible if required.

The patient perspective in malignant pleural effusion

The trials above have used symptoms and length of hospital stay as primary endpoints. An essential but completely understudied are in MPE is the day to day quality of life and experience of patients living with malignant pleural effusion. Small scale qualitative studies (n<15) in patients with MPE have been undertaken[5], showing patients' breathlessness improve directly following a pleural intervention, however improvement in activity levels were short lived and health anxiety and fatigue persisted. Further work is required in this area to understand the overall impact of the current MPE pathway and a proposed accelerated pathway, and these assessments form the core components of this study.

6. OBJECTIVES AND OUTCOME MEASURES

	Objectives	Outcome Measures
Primary	Feasibility of recruitment and data collection.	40 patients randomised 1:1 between the standard pathway and accelerated pathway proportion of eligible patients who agree to randomisation / data completeness / availability and participant completion.
Secondary	1. Mean change and standard deviation in breathlessness	1. 100mm VAS scores completed before and after the procedure and 3x weekly thereafter for 6 weeks
	2. Patient anxiety and depression	2. Hospital anxiety and depression score (HADS) weekly for 6 weeks
	3. Health Related Quality of Life	3. EQLQ-C30 questionnaire, EQ 5D-5L questionnaire weekly for 6 weeks
	4. Time to actionable histopathology /diagnosis	4. Cancer multi-disciplinary team consensus
	5. Healthcare utilisation	5. Number of pleural procedures and days in hospital post enrolment
	6. Assess the acceptability to patients of the accelerated pathway and patient priorities	6. Perform structured qualitative interviews with a proportion of patients in both the standard care arm and accelerated arm and those declining participation.
	7. Proportion of adverse events for both arms	7. Record agreed adverse events

Patient group	Patients with suspected malignant pleural disease, based on any of: presentation, imaging, prior asbestos exposure or history of malignancy:
Intervention(s)	First procedure as a pleural biopsy (local anaesthetic thoracoscopy if available or image guided biopsy if local constraints preclude thoracoscopy) AND Indwelling pleural catheter (IPC) insertion in a single procedure = the accelerated pathway
Comparator	Standard care pathway as defined by the current British Thoracic Society Guidelines, with first procedure as pleural aspiration only, followed by subsequent procedures for tissue biopsy and definitive fluid control

7. STUDY DESIGN

STREAMLINE is a prospective, up to three centre, randomised feasibility study of patients with a new, suspected malignant pleural effusion, who will be randomly allocated to receive either the accelerated pathway or standard care pathway (based on the BTS guideline 2010).

Patients randomised to the accelerated pathway will undergo a pleural procedure, a pleural biopsy + IPC insertion at their first visit. The pleural biopsy can be performed via either ultrasound guided pleural biopsy OR local anaesthetic thoracoscopy depending on local expertise, resource availability and managing clinical team decision making.

Patients randomised to the standard care pathway will be managed according to the updated 2023 BTS guidelines, which list pleural aspiration as the index procedure, followed by assessment of pleural fluid results and cytology, and progressing to pleural biopsy, IPC or talc pleurodesis as per MDT decision making and patient choice.

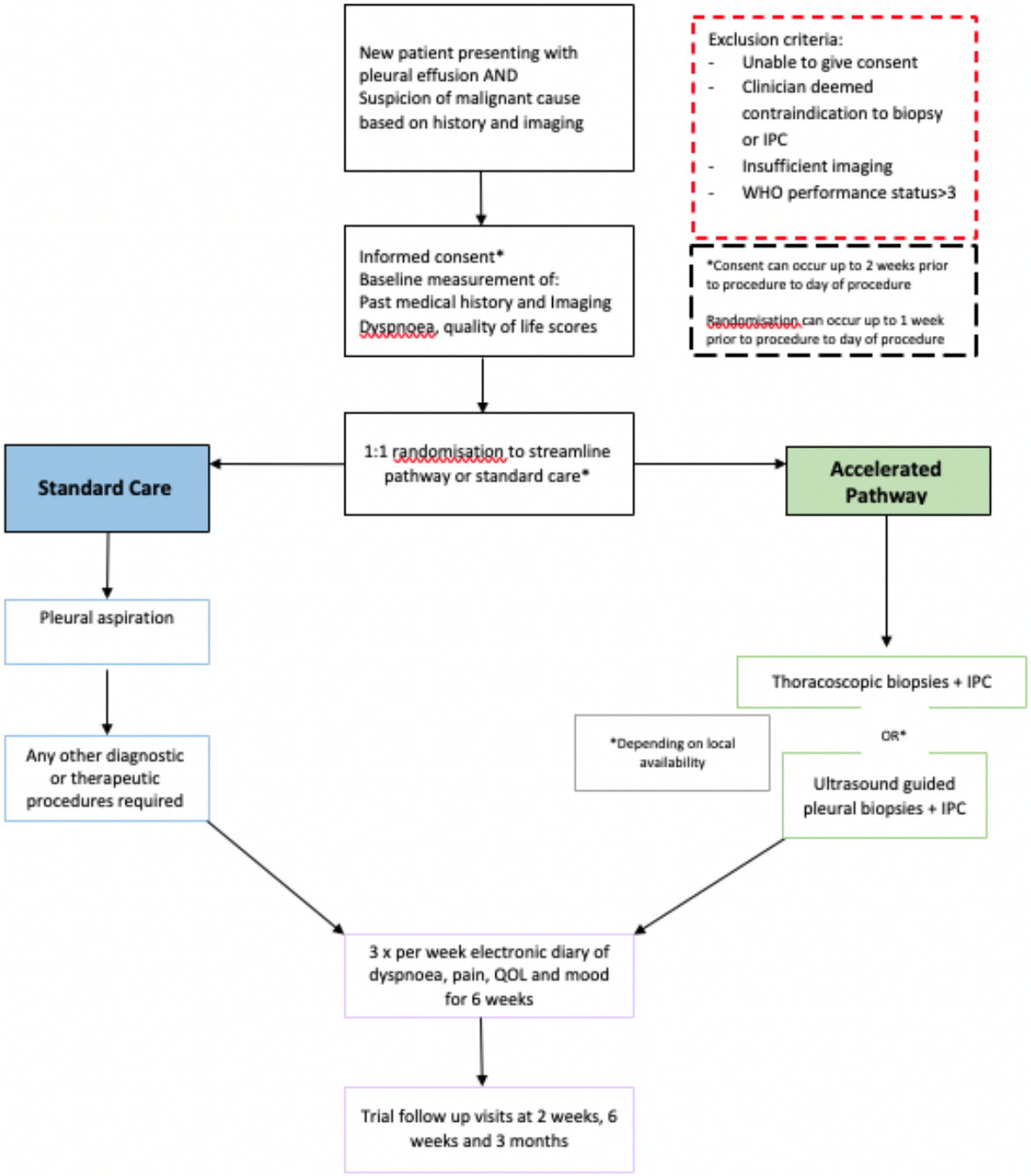

Figure 1: Diagram illustrating trial design and accelerated pathway
Key:
- Accelerated pathway
- Standard care pathway
- Assessment in both arms

We aim to recruit 40 patients Randomised 1:1 with probable MPE over an 18-month period with a 3 month follow up period. Patients will be typically recruited from their pleural clinic at each hospital in which each centre sees up to 20 patients with suspected MPE per month. The units perform an average of 12 procedures per week including 2 thoracoscopies and 2 ultrasound guided biopsies per week.

In-depth Participant Interviews
Qualitative interviews will be performed on a proportion of participants. These interviews will be performed by either the trial fellow or research nurse. Pseudonymised transcripts will be transcribed by an external transcription company. In addition, a proportion of those participants who refused randomisation but consented to be interviewed will also be approached to take part if willing, and, any themes arising from these two groups will be incorporated into the design of the subsequent definitive randomised controlled trial. The interviews will be performed either face to face, over the phone or via /audio conferencing. These recordings will be stored securely, electronically on the ORTU network drive before being sent to the transcription company. Once the transcription has is received these audio files will be deleted. Interviews will be conducted using participant ID's only, no names will be used during the interview.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Patients presenting for the first time with symptomatic unilateral pleural effusion with suspected malignant cause based on either: 1) History, imaging and clinical presentation or 2) Known other malignancy (but not yet proven to be the cause of pleural effusion by pleural aspirate cytology or pleural biopsy histopathology) l above the age of 18 years.

8.2. Inclusion Criteria

- Symptomatic unilateral (or bilateral if one side dominates) pleural effusion AND any of the following*
    - Suspicion of malignant cause based on imaging features on CT or ultrasound
    - Previous proven diagnosis of extrapleural malignancy
    - Lack of alternative likely clinical diagnosis such as infection or heart failure (as judged by local PI)
- Sufficient pleural effusion size as determined on ultrasound to require therapeutic pleural drainage.
- Participant is willing and able to give informed consent for participation in the trial.
- Male or Female, aged 18 years or above.

*The above features will be assessed by the local recruiting clinician, and judgments on likely clinical diagnosis and the imaging features will be conducted by local recruiting clinicians to remain pragmatic.

8.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Technically unable to undergo pleural biopsy and indwelling pleural catheter (e.g. gross respiratory failure, uncorrectable clotting, unable to tolerate position, poor performance status (WHO performance status 3 or worse when accounting for the effusion)).
- Visual impairment (precluding use of symptom measurement instruments[1,2]).
- Previous talc pleurodesis within the last 3 months on ipsilateral side.
- No means of phone contact
- Age <18 years
- Females who are pregnant or lactating

9. PROTOCOL PROCEDURES

The following table illustrates scheduled procedures and data collection

Procedures/assessments	Visits						
	Screening	Consent / Baseline / Randomisation	Day of Procedure	Follow up visits			
				Week 2	Week 6	Week 12	Adhoc clinical review as requiredy
		Up to -14 days	Day 0	± 3	± 3	± 7	
Eligibility assessment	X	X					
Informed consent		X					
Demographics and Medical History[R]	X	X					
Clinical assessment[R]	X	X	X	X	X		
Observations (vital signs) [R]		X	X	X	X		
Imaging Routine - Thoracic Ultrasound[R]		X	X	X	X		
Imaging Routine - Chest X-ray[1 R]	X	X	X	X	X		
Imaging Routine – CT Chest[R]	X						
Routine clinical bloods[R]		X[11]					
Concomitant medications[R]	X	X		X	X	X	
Randomisation		X					

IPC insertion			X[12]				X[6]
Pleural Biopsy			X[12]				X[5]
Therapeutic Aspiration			X[2]				
IPC drainage information			X[12]	X	X	X	X[7]
VAS-Dyspnoea and VAS-Pain			X[3]	X	X		
QOL: EQ5D, EORTC QLQ C30, HADS			X[4]	X	X	X	
Healthcare utilisation				X	X	X	
Adverse event assessments			X	X	X	X	
Time to histological diagnosis and systemic oncological treatment						X	X
Semi-structured interview[8]					X		X
Trial Nurse telephone call[9]							X
Ad Hoc Clinical Appointment							X

[1] A screening chest X Ray can be used as baseline if conducted within 2 weeks prior to first procedure.

[2]In standard care arm and as required throughout trial duration

[3]Self-reported VAS scores measured pre-and post procedure, 3 x per week from Day 0 to week 6

[4]Measured pre-procedure and 1/week for 6 weeks

[5]As required as part of 'standard care' arm

[6]As determined by patient and clinician choice in 'standard care arm', typically after confirmed histological diagnosis

[7]3 x per week

[8] At or after week 6 appointment

[9]Intermittently during the six weeks post intervention to ensure diary completion

[10] Patients may require urgent reviews or procedures due to symptoms -these can be delivered at any stage during the study as part of routine care

[11] Blood tests carried out up to four weeks prior to the initial procedure are accepted

[12] In accelerated arm only

[R]Indicates procedures or data collection that is part of routine care for all patients. The results of these are required to be collected and documented as part of the STREAMLINE study, hence are included in this table.

9.1. Recruitment

Patients will be identified by clinicians working in pleural services in the selected centres, from any part of the pleural service (inpatient, outpatient, day case). Patients identified as being eligible for enrolment will be approached by the clinical team responsible for their care (most likely to be the respiratory or pleural team) and provided with written information about the study.

9.2. Screening and Eligibility Assessment

Patients will be screened for eligibility from pleural procedure lists and pleural clinics. Any patient meeting the inclusion criteria will be approached for the study by the clinical team who will then contact the research team if a potential participant is interested in taking part.

Radiology (CXRs) taken as part of routine clinical care be used to screen for eligibility by confirming the presence of a pleural effusion. If no CXR is available, ultrasound may be used to screen (i.e. CXR is not a requirement for entry to the study). In all cases, ultrasound should be performed ***before randomisation*** (as part of routine clinical care) to ensure there is sufficient fluid to conduct a therapeutic intervention including indwelling pleural catheter.

Patients who decline participation in the study will have the reason for non-participation (if volunteered) in the trial recorded on the screening logs.

9.3. Informed Consent

Patients will be judged to have capacity to consent to the trial if they:

- Understand the purpose and nature of the trial.
- Understand what the trial involves, its benefits, risks and burdens.
- Understand the alternatives to taking part.
- Retain the information long enough to make an effective decision.
- Make a free choice.
- Make this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity).

The Participant Information Sheet (PIS) and Consent Form will be presented and explained to the participants detailing the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; any known adverse effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason, without their future care being affected, and with no obligation to give the reason for withdrawal. The PIS will also include information about optional interviews for patients.

Participation in the study will be discussed with the patient at the appropriate outpatient appointment or inpatient consultation, which will form part of their normal care pathway. Patients will be given

sufficient time, as determined by the patient, to consider study entry and the opportunity to question the researcher, their GP or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of participant dated signature and dated signature of a member of the research team. Due to the nature of the clinical presentation (i.e.. significant breathlessness requiring intervention), ***recruitment can occur*** from 2 weeks prior to first procedure up to and including the day of procedure as long as the patient has had sufficient time to consider their participation and provide meaningful consent.

As part of routine clinical discussions, participants with potential MPE undergoing pleural biopsy and IPC will be aware that there is a significant concern that their effusion is caused by an underlying cancer, with pleural biopsies required to confirm the diagnosis. All patients will need to consent to study inclusion prior to their first pleural procedure. This information will be included in the PIS. If clinical discussions about likely malignancy cause the patient to become distressed, the treating clinician may choose not to give further information about the STREAMLINE trial. In this situation the patient's details should be recorded on the screening log with reason for non-enrolment included.

Patients Declining to participate in STREAMLINE

Patients offered, but declining participation in the STREAMLINE study will be asked if they would be willing to participate in qualitative interviews so we can also gain information on the reasons for their non-participation. Consent for interviews will be undertaken via a separate consent form.

9.4. Randomisation

Once the participant has given written consent to the study, a member of the trial team, authorised and trained will randomise the participant to a treatment allocation. Consent can be given for randomisation up to 2 weeks before the randomisation event (with ongoing consent confirmed verbally with the patient).

In all cases, randomisation can occur on the day of procedure, or up to 1 week in advance to allow for planning of procedure lists.

Randomisation will occur 1:1 between the standard pathway and the accelerated pathway, and performed by sites using a web-based randomisation system, (Sealed Envelope - https://www.sealedenvelope.com/). Minimisation with a residual randomised component will occur with the following minimisation criteria:

- Known extrapleural malignancy or not
- Clinical suspicion of mesothelioma or not

9.5. Blinding and code-breaking

The trial will be unblinded due to the nature of interventions, so no un-blinding procedures are required.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

There are no investigational medicinal products in this trial with all interventions being standard medical practice. The interventions are described in the sections above with standard operating procedures for the interventions as part of this study.

Standard pathway: Patients will receive a therapeutic pleural aspiration as the first procedure as part of the 'standard care' pathway, and can receive thoracoscopic pleural biopsies, image guided pleural biopsies and IPC after the first intervention as determined by the clinical team.

Accelerated pathway: Patients in the accelerated arm will receive pleural biopsies (via either thoracoscopy or image guided) AND IPC as the first intervention. Further IPC management (frequency of drainage, use of talc via the IPC, IPC removal) will be at the discretion of the local investigator according to clinical need, and guided by a trial specific procedure (TSP).

Concomitant medication

All concomitant medications are permitted in this trial. Use of medications which are thought to reduce pleurodesis success (such as steroids) are permitted but will be recorded on CRFs. Talc for pleurodesis may be used as part of the standard care pathway and after the trial intervention in the accelerated pathway, as guided by a separate TSP.

9.7. Baseline Assessments

A baseline assessment will be performed by a member of the trials team and documented on the relevant CRF. Baseline data may be collected and entered onto the CRF up to 2 weeks prior to the planned trial procedure date. Baseline data will include:

- Confirmation of inclusion / exclusion criteria
- Participant demographics
- Relevant medical history including:
    - WHO performance status
    - Duration of symptoms at the point of recruitment
    - Type of malignancy (if a known history of malignancy)
    - Pleural interventions on ipsilateral side to date
    - Asbestos exposure history
- Radiology results from scans done as part of routine care (labelled 'routine' in schedule of procedures)
- Pre-procedure breathlessness and chest pain VAS –
- Pre-procedure quality of life assessments and HADS score
- Results of routine clinical blood tests from any time within 4 weeks pre-randomisation

Demographic data, medical history and baseline parameters for breathlessness, pain and quality of life/anxiety will be collected directly pre and post the first intervention. Recording of these parameters will continue on a 3 times per week basis for 6 weeks post initial intervention. Given the demographic of patients expected in the STREAMLINE study, participant facing forms (such as visual analogue scores and questionnaires) will be printed as part of a paper diary to complete at home after the first procedure. Clinician completed CRFs will be entered directly into electronic database. In depth qualitative interviews assessing patient acceptability and experience will be undertaken at or after the 6 week follow up.

Patients will then undergo the index procedure as dictated by randomisation – either pleural aspiration (standard pathway) or pleural biopsy + IPC (accelerated pathway)

- Oxford participants may also be approached and separately consented to gift pleural fluid samples to the Oxford Radcliffe Biobank.
- Following discharge patients will complete weekly VAS dyspnoea scores 3 times per week for 6 weeks and weekly quality of life scores via a paper diary.

9.8. Subsequent Visits

The follow up period is 12 weeks post procedure Trial follow up appointments will take place at

- 2 weeks ± 3 days
- 6 weeks ± 5 days and
- 12 weeks ± 7 days post procedure

This follow up schedule mirrors normal clinical care. Appointments should take place at the patient's local centre.

Data collected at each follow up will be:

1. VAS diary (week 2, 6 visit)

2. QLQ C30, EQ 5D 5L, and HADS diary (week 2, 6 visit)

3. Side effects attributable to the trial intervention

4. Information on healthcare utilisation including inpatient and outpatient admissions for pleural effusion management and any other cause

5. Ultrasound and Chest X Ray will be conducted at 2 weeks and 6 weeks as part of standard care, and results documented on the CRF.

At each follow up visit participants will undergo a standard clinical consultation, which should be conducted by a medical member of the trials team and the appropriate CRF should be completed. A chest x-ray (and ultrasound if available) should be performed (as per routine clinical care) and the results entered into the CRF. Participant completed diaries will be reviewed at these visits.

Participants will be asked to complete a home VAS diary three times per week and Quality of Life scores (1 per week) for 6 weeks post index procedure.

In light of the COVID-19 pandemic it is possible that participants and/or sites will judge that participant contact should be minimised. In recognition of this, follow up visits at 12 weeks may be carried out remotely via telephone.

Reasonable travel expenses to participants for visits that do not align with clinical care will be covered as part of the per participant costs. All feasible efforts have been made to align clinical and study visits, however, 'non-aligned' visits may occur in cases, for example whereby participants have required clinical review outside the study visits and thus are required to attend for a study visit sooner than otherwise required.

Visual Analogue Scale (VAS) scoring

VAS outcomes will be captured using participant paper diaries. Following hospital discharge, participants will receive a trial nurse phone call once per week, according to local availability, as a reminder to complete the VAS scores. The schedule of VAS scores is as follows:

- Pre-procedure VAS (day of first procedure, immediately prior).

- Post procedure VAS (day of the procedure, before discharge)
- Then thrice weekly for 6 weeks (participants will be advised to conduct this at a similar time each day to their convenience, on specified days, e.g. Monday / Wednesday / Friday).

Qualitative Interviews

Participants (consenting to be interviewed) will be approached for participation in qualitative interviews regarding their experiences during the study or their reasons for refusing inclusion/randomisation. This will aim to establish priorities of care and therefore important outcomes in the planned multicentre randomised controlled trial. It is anticipated that the interviews will take place at a scheduled follow up visit. The interviews will be undertaken by members of the research team trained in qualitative methodology.

9.9. Sample Handling

Samples for routine clinical care will be conducted as per local hospital practice. They do not play a part in the study or analysis.

Oxford participants may be approached separately to consent to have their pleural fluid removed as part of the procedure processed and stored as part of the Oxford Radcliffe Biobank.

9.10. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early from the study treatment at any time without having to give a reason and this will not affect their future care. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with study procedures
- Participant decision

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up.

Participants may withdraw their consent, meaning that they wish to withdraw from the study completely.

9.11. Definition of End of Study

The end of study declaration will occur at the time of final database lock.

10. SAFETY REPORTING

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2. Reporting procedures for AEs

The population of patients involved in STREAMLINE is one in which a high number of adverse events are expected due to the underlying likely disease (metastatic cancer), therefore only adverse events meeting the criteria to be a Serious Adverse Event will be recorded.

10.3. Reporting Procedures for Serious Adverse Events

Table of Anticipated Events

Given the comorbid nature of the patient population, the below table lists events that are anticipated in this population that do not require expedited reporting but will be captured in CRFs. Many of these will not be causally related to the investigational intervention, but rather will be a direct consequence of the patient's underlying malignancy. Other events may occur as a result of a trial-related intervention but are well-documented and regarded as normal complications of IPC use, thoracoscopy or pleural aspiration.

Relating to pleural intervention (aspiration, IPC, biopsy)	Pain requiring analgesia Hypotension Respiratory failure Fever Atrial fibrillation Haemorrhage Organ damage Postoperative pneumothorax or air leak Bronchopleural fistula Pneumonia Hospital admission Empyema Subcutaneous emphysema Failure to reach a diagnosis Operative skin site infection Port site tumour growth

	Organ damage Respiratory failure Pleural infection IPC blockage Failure of IPC requiring replacement Catheter tract metastasis
Relating to underlying malignancy	Death related to underlying malignancy Recurrent pleural fluid Surgery or procedure related to underlying malignancy or pleural fluid recurrence Malignancy treatment related side effects (including chemotherapy and radiotherapy side effects e.g. neutropaenic sepsis)

The **safety reporting period** is for **6 weeks post initial procedure**, or **until IPC removal** (if removed prior to 6 weeks – i.e. whichever is sooner).

SAEs that are considered (by the site investigator) to be **possibly, probably or definitely related** to the study intervention (i.e. the procedure conducted for the study) **and not an anticipated event** (Appendix A) will be reported on the relevant reporting form (PM124-A Serious Adverse Event Report Form (non-CTIMPs)) and emailed to ORTU without delay. ORTU will perform an initial check of the report, request any additional information, ensure it is reviewed by a nominated Medical Reviewer.

Any anticipated SAE or SAE considered **not related** to the study intervention by the local investigator does not require expedited reporting but will be recorded on the appropriate procedure, discharge or follow up CRF.

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The plan for the statistical analysis of the trial are outlined below. There is no separate SAP document in use for the trial.

11.2. Description of the Statistical Methods

Outcome Measures

We will adopt clear criteria for progression to a large-scale clinical study. If all criteria are met (green) we will proceed to apply for future funding for a full clinical study with the same protocol; if one or more

criteria is amber, we will adapt the protocol to address the shortfall and re-assess, and any red criteria will prompt major changes to study design or non-progression.

The major feasibility outcomes are as below (includes all sites) and are to be applied once all centres are actively recruiting:

	Green	Amber	Red
1. Average monthly recruitment (pts / month)*	≥1.5	0.5-1.5	<0.5
2. Proportion of data completion (VAS, QOL) in those capable of completing (i.e. not including those who have died during trial follow up)	³90%	75%-90%	<75%
3. Data availability - time to diagnosis	≥90%	75%-90%	<75%
4. Proportion completing study protocol in those who are still alive at end of follow up	≥90%	80-90%	<80%
5. Proportion of eligible patients randomised	>50%	30-50%	<30%

*Once all centres have been greenlighted

In depth screening logs will be maintained at recruiting centres, in order to calculate the proportion of eligible patients and the proportion accepting randomization to the study protocol. A patient is considered to be eligible if they fulfil all of the inclusion criteria and none of the exclusion criteria. Screening logs will be reviewed by the central trial team on a monthly basis once all centres have been greenlighted.

Secondary outcomes:

- Mean change and SD in 100mm visual analogue score for breathlessness. This is the current proposed primary outcome measure for a definitive clinical trial and will be measured over follow up.
- Time to actionable histopathology (MDT consensus, referral for oncological treatment)
- Healthcare utilization – number of pleural procedures over 3 months follow up
- Patient anxiety and depression over the diagnostic pathway period (hospital anxiety and depression score (HADS), quality of life by QLQ-C30 tool)
- All-cause mortality (retrospective electronic patient record review)

Data and Statistical Analysis

Feasibility parameters will be analysed for the overall trial and for each individual arm of the trial. The mean / median and variability of each major outcome will be calculated, to power a potential future definitive study.

Initial comparisons between randomised groups will be conducted for the major outcome measures to assess for early signals. Data will be analysed with the assistance of a dedicated statistician (Dr Ly-Mee Yu) using a mixed effects regression model to account for repeated sampling over 3 months.

Qualitative Interview Analysis

Structured qualitative interviews will be thematically analysed. The trial fellow (DA) with consultancy provided by the specialist qualitative team at Oxford Brookes University will undertake inductive coding to develop a coding framework. code lists before applying them to the entire dataset. Coded elements of the interview transcripts will be combined into categories and themes identified from patterns in the dataset for reporting.

11.3. Sample Size Determination

As a feasibility study, sample size has not been formally calculated. However, other feasibility studies looking at interventions in MPE have typically used 30 to 50 participants[22 23].

In a potential future definitive study of the accelerated pathway, mean difference in VAS (for which the MCID is 19mm) would be a likely primary outcome measure. In such a study, 170 participants would be sufficient to detect a mean difference of 19mm between the two arms (5% significance, 90% power) assuming an SD of 35mm based on previous MPE studies[7].

If a quality of life measurement was preferred as the primary outcome, the MCID in global health status based on reference values provided by the EORTC Quality of Life Group is 8 points.190 patients would achieve a 90% power to detect an 8 point difference[24 25] with a common SD within group of 23.6, derived from EORTC reference values.

Thus, in a future 8-centre study, a recruitment target of 190 patients (powered for VAS or QOL) could be achieved in 18 months if recruitment occurs at approximately 1-2 participants per centre per month. **Therefore, the recruitment target for our proposed feasibility study is 1-2 participants per month.**

We propose 40 patients to allow for 10% attrition and based on likely recruitment rate within the study timetable.

11.4. Analysis populations

The study will be analysed on intention to treat, with included populations as specified above.

11.5. Decision points

No interim analysis will be conducted. The Study Steering Committee will review the recruitment rate regularly throughout the study.

11.6. Stopping rules

No formal stopping rules are planned.

11.7. The Level of Statistical Significance

N/A

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data will be reported for the key feasibility and clinical outcomes, but no adjustment will be undertaken.

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any changes/deviations from the statistical analysis outlined here will be described and justified in the final statistical report.

11.10. Health Economics Analysis

Initial Health Economic Analysis will be undertaken, to inform a potential larger trial, and will be the subject of a specific Health Economic Analysis plan to be written during trial recruitment, using the parameters collected.

12. DATA MANAGEMENT

12.1. Source Data

Source documents are where data are first recorded. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be obtained, and include electronic patient records), clinical and office charts, laboratory and pharmacy records, and medical imaging.

Data required for the conduct and analysis of this study will be collected via paper participant facing paper diaries and clinician entered electronic CRFs (e-CRFs). This may be transcribed or summarised from source documents, or may be collected directly in trial e-CRFs. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no previous written or electronic record of data).

Audio files will be stored by the sponsor and sent securely to the external transcription company. Once the transcript is received, these files will be permanently deleted.

Consent forms retained for those participants consenting to be contacted for future research (Oxford participating site only) will be stored securely at the Oxford Respiratory Trials Unit.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12.3. Data Recording and Record Keeping

Data will be entered into a secure, validated, GCP-compliant electronic data management system. All staff performing data entry will be appropriately trained prior to access being granted. Access is controlled by individual user accounts, and a full audit trail is kept of all modifications made to data.

Standard Operating Procedures (SOPs) will be followed to maximise completeness and accuracy of trial data. The processes for quality assurance of study data will be detailed in the study monitoring plan, data management plan, and other associated documents.

Participants will only be identified in all study documents and datasets (other than the signed consent form) by a unique trial-specific number or code. The name and any other identifying detail will NOT be included in any trial data electronic file.

Participants who consent to qualitative interviews will require their contact information to be sent to ORTU by a research nurse at the recruiting site to allow co-ordination of in-depth interviews.

All study documents will be stored securely. Both paper and electronic study data will be retained through an archiving service for a period as described in the Data Management Plan.

13. QUALITY ASSURANCE PROCEDURES

13.1. Risk assessment

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

Monitoring for this study will be determined and documented within the study risk assessment.

13.3. Study Committees

Study Management Group

Study Management Group will meet regularly throughout the trial to discuss the day to day management of the study. A SMG charter will be written detailing all of the requirements:

Study Steering Committee

The Study Steering Committee will meet on a 6-monthly basis throughout the trial to assess the progress of the study. An SSC charter will be written detailing the requirements of this committee and its members.

Safety Oversight Group

The Oxford Respiratory Trials Unit (ORTU) Safety Oversight Group will conduct a review of all SAEs for the trial reported during the reporting period and cumulatively. The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or IMP administration) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file.

The Oxford Respiratory Trials Unit has Standard Operating Procedures for deviations and breaches which will be used throughout.

15. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

Eligible participants will be given detailed information and the opportunity to discuss the trial further with a member of the trial team. Participants are generally given 24 hours 'thinking time' thereafter to consider enrolling in a trial. It is recognised that clinical circumstances in this trial are likely to make this impossible. The participants will be asked to consent to study entry, the collection of information about their care, and collection of subsequent data sheets. All will be appropriately de-identified.

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

The trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

16.7. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the CRF and patient diary, where participant initials may be added. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018.

16.8. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

17. FINANCE AND INSURANCE

17.1. Funding

The study is funded by an NIHR doctoral fellowship (Dr Dinesh Addala).

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The preparation of a manuscript for rapid publication will be a priority for and sole responsibility of the Trial Management Group, under the overall supervision of the Chief Investigator. The Trial Management Group will also take responsibility for reviewing drafts of any manuscripts, abstracts, press releases and other publications arising from this study. It is anticipated that an initial report would be completed within six months of the study's closure. The Trial Management Group will approve a definitive manuscript detailing the final overall results of the study. Raw data from the study will be made accessible to the public on request once the study has been completed and final results been published. The trial will be registered on the ISRCTN public access database.

All publications will include a list of investigators, and named authors will include the study's Chief Investigator, Key Investigator(s), Statistician and Trial Manager as a minimum. Authors will be determined in accordance with ICMJE guidelines and other contributors to the study will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

N/A

20. ARCHIVING

Sites will be required to archive their own documentation within their local institution. All CTU trial documentation will be archived in accordance with ORTU SOP's.

21. REFERENCES

1. Villanueva AG. Management of Malignant Pleural Effusions. *Principles and Practice of Interventional Pulmonology*. Published online May 22, 2012:665-674. doi:10.1007/978-1-4614-4292-9_64

2. Scherpereel A, Astoul P, Baas P, et al. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. *European Respiratory Journal*. 2010;35(3):479-495. doi:10.1183/09031936.00063109

3. Bibby AC, Dorn P, Psallidas I, et al. ERS/EACTS statement on the management of malignant pleural effusions. *European Respiratory Journal*. 2018;52(1). doi:10.1183/13993003.00349-2018

4. Penz E, Watt KN, Hergott CA, Rahman NM, Psallidas I. Management of malignant pleural effusion: challenges and solutions. *Cancer Manag Res*. 2017;9:229-241. doi:10.2147/CMAR.S95663

5. Twose C, Ferris R, Wilson A, Rahman N, Farquhar M, Mishra E. Therapeutic thoracentesis symptoms and activity: a qualitative study. *BMJ Supportive & Palliative Care*. Published online January 8, 2021. doi:10.1136/bmjspcare-2020-002584

6. Mercer R, Varatharajah R, Shepherd G, et al. Critical analysis of the utility of initial pleural aspiration in the diagnosis and management of suspected malignant pleural effusion. *BMJ open respiratory research*. 2020;7. doi:10.1136/bmjresp-2020-000701

7. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA*. 2012;307(22):2383-2389. doi:10.1001/jama.2012.5535

8. Effect of an Indwelling Pleural Catheter vs Talc Pleurodesis on Hospitalization Days in Patients With Malignant Pleural Effusion: The AMPLE Randomized Clinical Trial | Breast Cancer | JAMA | JAMA Network. Accessed January 4, 2022. https://jamanetwork.com/journals/jama/fullarticle/2664042

9. implementing-timed-lung-cancer-diagnostic-pathway.pdf. Accessed December 31, 2021. https://www.england.nhs.uk/wp-content/uploads/2018/04/implementing-timed-lung-cancer-diagnostic-pathway.pdf

10. Penz ED, Mishra EK, Davies HE, Manns BJ, Miller RF, Rahman NM. Comparing cost of indwelling pleural catheter vs talc pleurodesis for malignant pleural effusion. *Chest*. 2014;146(4):991-1000. doi:10.1378/chest.13-2481

11. Botana Rial M, Leiro Fernández V, Represas Represas C, Pallarés Sanmartín A, Del Campo Pérez V, Fernández-Villar A. [Cost-effectiveness study of the diagnosis of pleural effusion in chest diseases outpatient clinic]. *Arch Bronconeumol*. 2010;46(9):473-478. doi:10.1016/j.arbres.2010.05.010

12. Arnold DT, De Fonseka D, Perry S, et al. Investigating unilateral pleural effusions: the role of cytology. *Eur Respir J*. 2018;52(5):1801254. doi:10.1183/13993003.01254-2018

13. Tsim S, Paterson S, Cartwright D, et al. Baseline predictors of negative and incomplete pleural cytology in patients with suspected pleural malignancy – Data supporting 'Direct to LAT' in selected groups. *Lung Cancer*. 2019;133:123-129. doi:10.1016/j.lungcan.2019.05.017

14. Overview | Lung cancer: diagnosis and management | Guidance | NICE. Accessed January 4, 2022. https://www.nice.org.uk/guidance/ng122

15. Ahmadzada T, Kao S, Reid G, Boyer M, Mahar A, Cooper WA. An Update on Predictive Biomarkers for Treatment Selection in Non-Small Cell Lung Cancer. *J Clin Med*. 2018;7(6):153. doi:10.3390/jcm7060153

16. Sconfienza LM, Mauri G, Grossi F, et al. Pleural and peripheral lung lesions: comparison of US- and CT-guided biopsy. *Radiology*. 2013;266(3):930-935. doi:10.1148/radiol.12112077

17. Baas P, Fennell D, Kerr KM, et al. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26 Suppl 5:v31-39. doi:10.1093/annonc/mdv199

18. Rahman NM, Pepperell J, Rehal S, et al. Effect of Opioids vs NSAIDs and Larger vs Smaller Chest Tube Size on Pain Control and Pleurodesis Efficacy Among Patients With Malignant Pleural Effusion: The TIME1 Randomized Clinical Trial. *JAMA*. 2015;314(24):2641-2653. doi:10.1001/jama.2015.16840

19. Tremblay A, Mason C, Michaud G. Use of tunnelled catheters for malignant pleural effusions in patients fit for pleurodesis. *Eur Respir J*. 2007;30(4):759-762. doi:10.1183/09031936.00164706

20. Wahidi MM, Reddy C, Yarmus L, et al. Randomized Trial of Pleural Fluid Drainage Frequency in Patients with Malignant Pleural Effusions. The ASAP Trial. *Am J Respir Crit Care Med*. 2017;195(8):1050-1057. doi:10.1164/rccm.201607-1404OC

21. Muruganandan S, Azzopardi M, Fitzgerald DB, et al. Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2): an open-label randomised trial. *The Lancet Respiratory Medicine*. 2018;6(9):671-680. doi:10.1016/S2213-2600(18)30288-1

22. Martin GA, Tsim S, Kidd AC, et al. Pre-EDIT: A Randomized Feasibility Trial of Elastance-Directed Intrapleural Catheter or Talc Pleurodesis in Malignant Pleural Effusion. *Chest*. 2019;156(6):1204-1213. doi:10.1016/j.chest.2019.07.010

23. Papworth Hospital NHS Foundation Trust. *MesoTRAP: A Pilot Clinical Trial and Feasibility Study Comparing Video-Assisted Thoracoscopic Partial Pleurectomy/Decortication With Indwelling Pleural Catheter in Patients With Trapped Lung Due to Malignant Pleural Mesothelioma Designed to Address Recruitment and Randomisation Uncertainties and Sample Size Requirements for a Phase III Trial.* clinicaltrials.gov; 2020. Accessed January 3, 2022. https://clinicaltrials.gov/ct2/show/NCT03412357

24. King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. *Qual Life Res*. 1996;5(6):555-567. doi:10.1007/BF00439229

25. Sivakumar P, Douiri A, West A, et al. OPTIMUM: a protocol for a multicentre randomised controlled trial comparing Out Patient Talc slurry via Indwelling pleural catheter for Malignant pleural effusion vs Usual inpatient Management. *BMJ Open*. 2016;6(10):e012795. doi:10.1136/bmjopen-2016-012795

22. Appendix A: Amendments

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC / HRA submission.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).