The Meso-ORIGINS Feasibility Study

STUDY PROTOCOL

Planned Study Period:	12 months
Planned Study Start Date:	1st December 2018
Sponsor:	NHS Greater Glasgow & Clyde
Sponsor Representative:	joanne.mcgarry@ggc.scot.nhs.uk
Sponsor Ref:	GN17ON341
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The June Hancock Mesothelioma Research Fund

Glasgow Clinical Research Facility

Glasgow Pleural Disease Unit

Table of Contents

1 Abbreviations

AE	Adverse Events
BAPE	Benign Asbestos Pleural Effusion
BTS	British Thoracic Society
CI	Chief Investigator
CL	Confidence Interval
CRF	Case Report Forms
CRP	C-Reactive protein
CT	Computed Tomography
CTU	Clinical Trials Unit
CXR	Chest X-Ray
DNA	Deoxyribonucleic Acid
IPC	Indwelling Pleural Catheter
LAT	Local Anaesthetic Thoracoscopy
LHD	Lactate Dehydrogenase
MDT	Multi-disciplinary Team Meeting
MPM	Malignant Pleural Mesothelioma
NHS	National Health Service
PACS	Picture Archiving and Communications Systems
PIS	Patient Information Sheet
PI	Principle Investigator
PM	Pleural Malignancy
QEUH	Queen Elizabeth University Hospital
RES	Research Ethics Committee
ROS	Reactive Oxygen Species
SAE	Serious Adverse Events
TUS	Thoracic Ultrasound
VATS	Video-assisted Thoracoscopic Surgery

2 Synopsis

Study Title	The Meso-ORIGINS Feasibility Study
Study Design	Multi-centre prospective feasibility study incorporating a retrospective multi-centre cohort study
Study Participants	Patients with Benign Asbestos Pleural Effusion (BAPE)
Sample Size	Prospective observational study: n = 54 (or n=27 feasible patients, whichever is reached first). Retrospective cohort study: n=300
Study Period	12 months
Sponsor	NHS Greater Glasgow & Clyde
Background and Rationale	MPM typically develops 30-50 years after inhalation of asbestos and is often presaged by radiological +/- clinical evidence of chronic pleural inflammation, and frequently by overt pleural effusion. The base agnostic pattern of DNA damage recently reported in MPM also suggests a prominent role for immune or inflammatory triggers. However, the recent genomic characterisation of MPM (1) poses major questions regarding the pressures that drive MPM evolution, being dominated by loss of tumour suppressors, with few protein-altering mutations in known oncogenes (1). Greater understanding of the driving (oncogenic) +/- permissive (immunological) events is required to design effective MPM treatments. In a future study called Meso-ORIGINS, we aim to define *in vivo* the key biological events that drive or permit evolution of MPM. Meso-ORIGINS will involve serial biological surveillance (using circulating markers, imaging +/- repeat pleural fluid and biopsies) over a 2-year period preceding the diagnosis of MPM. This will be achieved by recruitment of 850 patients with BAPE, of whom an estimated 12% (n=100) will develop MPM based on previous data (2). This will facilitate unprecedented surveillance of the key early biological events in MPM tumourigenesis. The current feasibility study will address important areas of uncertainty regarding the current Meso-ORIGINS design, including: • *within a prospective feasibility study,* the technical feasibility and patient acceptability of a surveillance protocol including LAT, and alternative strategies limited to blood tests, imaging +/- pleural fluid sampling • *within a retrospective cohort study,* greater precision regarding the sample size estimate (currently n=850). This is based on a single study that reported a 2-year MPM transition rate of 12% (95%CI 4.5% - 26.4%) (2). If the true rate is close to the lower end of this 95% CI this may mandate an unfeasible sample size.

	Trial Objectives	Associated End-points
Prospective Feasibility Study	**Primary Objective:** To determine whether it will be possible to recruit sufficient numbers of eligible patients in a reasonable time frame to Meso-ORIGINS based on the currently proposed surveillance protocol (involving LAT)	**Primary End-point:** Feasibility, defined as the ability to recruit 27 patients over 12-months (or 14 patients over any 6-month period) meeting the following criteria: • They satisfy all Meso-ORIGINS eligibility criteria (see below) • They deem the proposed thoracoscopic surveillance program acceptable (see *Patient Acceptability Questionnaire*) • Their study team deem that at least one LAT at/before 6 months is technically feasible (see *LAT Technical Feasibility*
	Secondary Objective: To explore reason(s) for declining consent to surveillance and the acceptability to patients of less invasive surveillance protocols (not involving repeat LAT)	**Secondary End-point:** Results of a *Patient Acceptability Questionnaire* including hypothetical consent for alternative surveillance strategies, including: • Blood Tests • Breath sampling • Pleural fluid sampling • Imaging only (CXR, CT, MRI)
Retrospective Cohort Study	**Primary Objective:** To determine more precisely the rate of transition to MPM in patients diagnosed with BAPE	**Primary End-point:** The rate of MPM transition, defined as the number of eligible patients diagnosed with MPM within 2 years of the diagnosis of BAPE divided by the total number of eligible patients.
	Secondary Objective: To identify baseline predictors of transition to MPM, allowing refinement of the current Meso-ORIGINS eligibility criteria	**Secondary End-point:** A logistic regression model for MPM transition using baseline data as predictors

<table>
<tr><td>Eligibility Criteria</td><td>Prospective Feasibility study Inclusion Criteria:
• History of asbestos exposure or compatible imaging e.g. pleural plaques
• CT imaging compatible with BAPE or compatible histological diagnosis at biopsy including any of the following: benign fibrinous pleurisy, non-specific pleuritis or atypical mesothelial proliferation
• Informed written consent
• Prognosis ≥6months

Retrospective Cohort study Inclusion Criteria:
• Histological diagnosis compatible with BAPE including benign fibrous pleurisy, non-specific pleuritis or atypical mesothelial proliferation
• ≥2 years follow-up completed at the point of enrolment</td></tr>
<tr><td></td><td>Exclusion Criteria:
• Histo-/cytological diagnosis of MPM or secondary pleural malignancy
• Pleural infection, empyema or granulomatous pleuritis
plus for the Retrospective Cohort Study only:
< 2 years follow-up completed at the point of enrolment</td></tr>
<tr><td>Prospective Feasibility Study
Recruitment, Study Visits & Follow up</td><td>Potentially eligible patients will be approached at outpatient clinic, any time after a diagnosis of BAPE (this can be a radiological diagnosis). All study visits will be combined with clinic attendances, where possible:

<table><tr><th>Visit</th><th>Timing</th><th>Study Interventions</th></tr><tr><td>Visit 1</td><td>Day 0</td><td>Provision of PIS
Consent, Registration
Baseline CRF</td></tr><tr><td>Visit 2</td><td>2-6 months
(+/-2 weeks)</td><td>Follow-up CRF
Acceptability Questionnaire</td></tr></table>
If patient recruited ≥6months after initial BAPE diagnosis then visit 2 can be combined with visit 1 on day 0.</td></tr>
<tr><td>Retrospective Cohort Study
Case Selection and Data Collection</td><td>The following data will be recorded retrospectively for all eligible patients using LAT, VAT and ultrasound guided biopsy databases, and electronic health records at the study centres. A data collection form (.xls) will be provided. All data will be recorded in a linked anonymised format.
• Baseline clinical data (e.g. imaging, blood results, LAT data)
• Follow-up data, including any diagnosis of MPM within 2 yrs</td></tr>
<tr><td>Approvals</td><td>Research Ethics Committee (REC) approval will be sought. Informed written consent will be documented in all Prospective Feasibility Study participants. Caldicott (or equivalent) local approvals will be sought for use of unconsented data in the Retrospective study.</td></tr>
</table>

Reimbursement to Sites	Sites will be reimbursed on a per patient basis (£25 per patient completing all prospective study visits, £2 per patient with complete data collection in the retrospective study).
End of Study	Recruitment to the prospective study will terminate after 54 patients have been recruited, after 27 patients have met the primary end-point, or 12 months after study opening, whichever is soonest. The study will end after the last prospective study patient has completed Visit 2.

3 Research Team and Contact Details

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4 Abstract and Study Design

4.1 Abstract

MPM typically develops 30-50 years after inhalation of asbestos fibers and is often presaged by radiological and/or clinical evidence of asbestos-related chronic pleural inflammation, and frequently by overt pleural effusion. The base agnostic pattern of DNA damage recently reported in MPM also suggests a prominent role for immune or inflammatory triggers. However, the recent genomic characterisation of MPM (1) poses major questions regarding the pressures that drive MPM evolution, being dominated by loss of tumour suppressors, with few protein-altering mutations in known oncogenes (1). Greater understanding of the driving (oncogenic) +/- permissive (immunological) events is required to design effective MPM treatments.

In a future study called Meso-ORIGINS, we aim to define *in vivo* the key biological events that drive or permit evolution of MPM. Meso-ORIGINS will involve serial biological surveillance (using a protocol involving circulating markers, imaging +/- repeat pleural fluid and biopsies) over a 2-year period preceding the diagnosis of MPM. This will be achieved by recruiting approx. 850 patients with Benign Asbestos Pleural Effusion (BAPE), of whom an estimated 12% (n=100) will develop MPM based on previous data (2). This will facilitate unprecedented surveillance of the key early biological events in MPM tumorigenesis. These will be interrogated for mechanisms and potential druggable targets in a genetically engineered mouse model (GEMM) integrated into the Meso-ORIGINS program.

The current feasibility study will address important areas of uncertainty regarding the current Meso-ORIGINS design, including the technical feasibility and patient acceptability of the proposed surveillance protocol (including Local Anaesthetic Thoracoscopy (LAT)) and the sample size estimate. Alternative strategies for surveillance for transformation to MPM will be explored including imaging, blood tests for biomarkers (3, 4) and breath tests (5, 6, 7). The objectives of the feasibility study are as follows:

Primary: To determine whether it will be possible to recruit sufficient numbers of eligible patients in a reasonable time frame to Meso-ORIGINS based on the currently proposed surveillance protocol (involving LAT)

Secondary: To define the sample size estimate for Meso-ORIGINS more precisely

4.2 Lay Summary

Mesothelioma is a cancer most commonly affecting the tissue layers which line the lung and inside of the chest wall (the pleura). It most commonly presents with a collection of fluid surrounding the lung (pleural effusion). Mesothelioma is strongly associated with asbestos exposure, which causes intense inflammation of the pleura, but does not occur until many decades after exposure. Benign Asbestos Pleural Effusion (BAPE) is a non-cancerous condition also associated with asbestos exposure and pleural effusion. However, approximately 12% of patients diagnosed with BAPE

are subsequently diagnosed with Mesothelioma. It is not currently known what triggers the change from benign pleural inflammation to Mesothelioma. The Meso-ORIGINS study aims to define this by performing 2 years of surveillance, collecting measurements from repeat pleural fluid and biopsy samples, repeat blood tests and scans. The aim of this study, the Meso-ORIGINS feasibility study, is to determine whether it will be possible to recruit sufficient numbers of patients to Meso-ORIGINS and to work out whether it will possible to perform all of the repeat tests that might be helpful (including biopsies) and whether patients would agree to have these performed.

4.3 Study Design

4.3.1 Study Type

The primary objective will be assessed in a prospective observational study. The secondary objective will be assessed in a retrospective cohort study

4.3.2 Disease and Patient Group Studied

Patients with Benign Asbestos-related Pleural Effusion (BAPE)

4.3.3 Study Centres

The Meso-ORIGINS feasibility study will be a multi-centre prospective feasibility study, incorporating a retrospective multi-centre cohort study. The lead centre will be the Glasgow Pleural Disease Unit, QEUH, Glasgow.

4.3.4 Study Duration

The planned study duration is 12 months. Recruitment to the prospective feasibility study will terminate after 54 patients have been recruited, after 27 patients have been met the primary end-point regarding feasibility, or 12 months after the study opens, whichever is soonest. The prospective study will end once the final patient recruited has completed their 6 month follow up visit (Visit 2).

4.3.5 Study Sponsor

The study is sponsored by NHS Greater Glasgow & Clyde.

4.3.6 Study Funding

This study is part-funded from a grant provided by the June Hancock Mesothelioma Research Fund, part-funded by the Glasgow Clinical Research Facility and part-funded by the Chief Investigator.

4.4 Prospective Feasibility Study Objectives and End-points

4.4.1 Prospective Study Objectives

The primary objective is to determine whether it will be possible to recruit sufficient numbers of eligible patients in a reasonable time frame to Meso-ORIGINS, based on the currently proposed surveillance protocol (involving LAT).

The secondary objective is to explore reason(s) for declining consent to surveillance and the acceptability to patients of less invasive surveillance protocols (not involving LAT)

4.4.2 Prospective Study End-points

The **Primary End-point** shall be Feasibility, defined as the ability to recruit 27 patients from 4 centres over 12-months (or 14 patients over any 6-month period) meeting the following criteria:

a) They satisfy all Meso-ORIGINS eligibility criteria (see below)
b) They deem the proposed thoracoscopic surveillance program acceptable (see ***4.4.2.1 Patient Acceptability*** below)
c) Their study team deem that at least one LAT at/before 6 months is technically feasible (see ***4.4.2.2 LAT Technical Feasibility*** below)

This recruitment rate is equivalent to 6.8 patients/centre/year, based on the assumptions that 850 patients will be required for adequate signature differentiation in Meso-ORIGINS and 25 centres will recruit (similar to the DIAPHRAGM study (3)) over 5 years.

It is not considered ethical to directly test feasibility by fully executing the proposed surveillance protocol until the study has proven deliverable, particularly with regard to sample size (*see Retrospective Cohort Study*). Therefore, patient acceptability and technical feasibility will be assessed indirectly.

4.4.2.1 Patient Acceptability

To address this aspect of feasibility, a simple questionnaire will be used to record whether patients would hypothetically consent to LAT (or repeat LAT in some cases) for research purposes.

To address the **Secondary Objectives,** reasons for declining consent will be explored and hypothetical consent sought for alternative surveillance strategies, including:

- Blood Tests
- Breath Sampling
- Imaging (Chest X-ray, MRI, CT)
- Pleural Fluid sampling

4.4.2.2 LAT Technical Feasibility

This will be assessed using established sonographic markers (8) and defined as:

- Sufficient* pleural fluid to allow safe LAT access *or*
- Sufficient* lung-sliding to allow pneumothorax induction prior to LAT

**In the opinion of the site PI who would perform the LAT*

Detailed information regarding recommended ultrasound assessment will be provided for each site.

Note that ultrasound-directed cutting pleural biopsy (9) would be an alternative in Meso-ORIGINS if LAT was not possible. Therefore feasibility of this will be recorded.

4.5 Retrospective Cohort Study Objectives and End-points

4.5.1 Retrospective Cohort Study Objectives

The primary objective is to determine more precisely the rate of transition to MPM in patients diagnosed with BAPE.

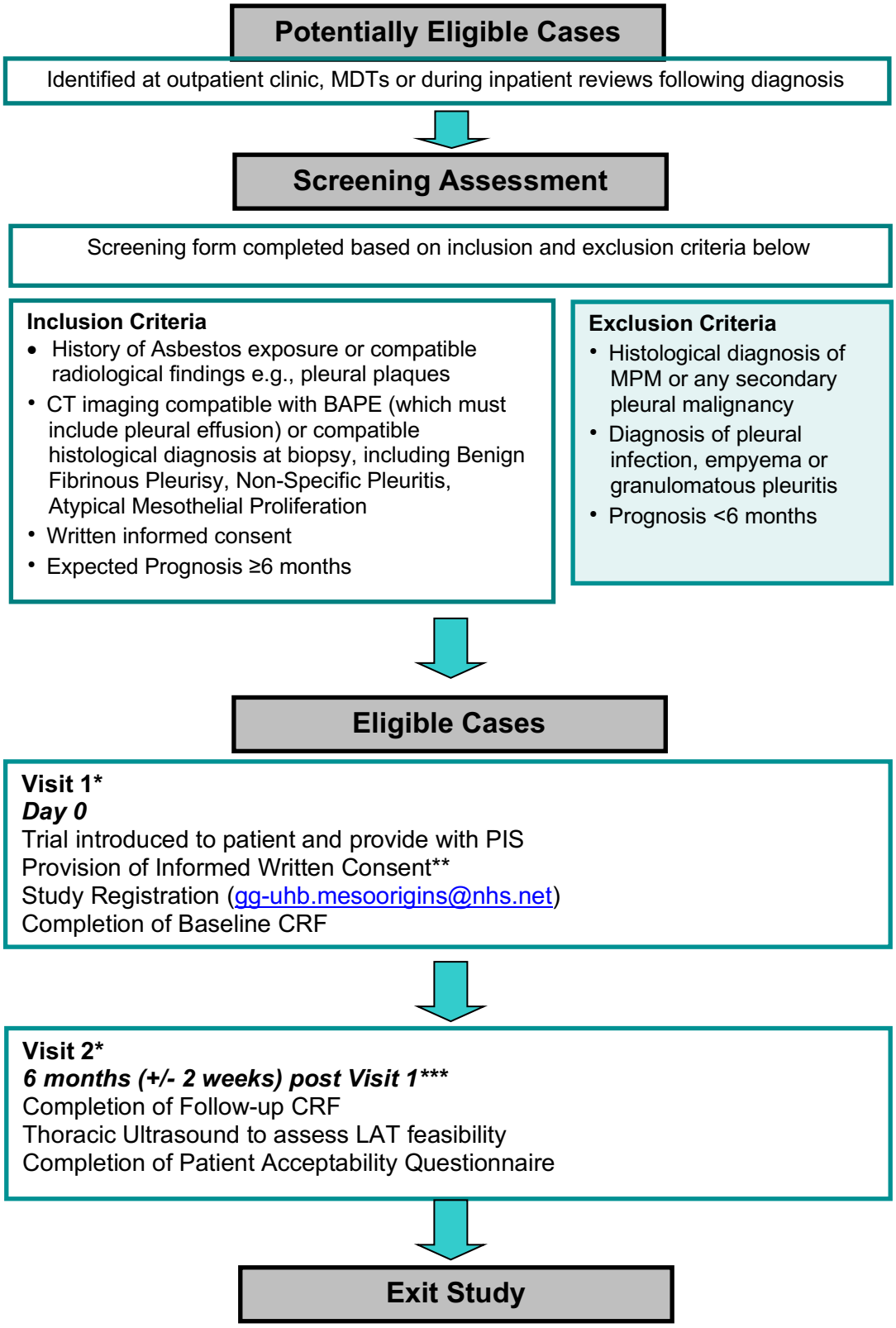
The secondary objective is to identify baseline predictors of transition to MPM, allowing refinement of the current Meso-ORIGINS eligibility criteria

4.5.2 Retrospective Cohort Study End-points

The **Primary End-Point** shall be the rate of MPM transition, defined as the number of eligible patients diagnosed with MPM within 2 years of the index diagnosis of BAPE divided by the total number of eligible patients.

The **Secondary End-Point** shall be a logistic regression model for MPM transition using baseline data as predictors.

4.6 Trial Flow Chart – Prospective Feasibility Study



Combined with routine clinic attendance
*** Provide another opportunity for patients to provide consent if required*
**** Can occur as early as 2 month following biopsy if symptomatic recurrence of pleural effusion or any other manifestation of progressive ipsilateral pleural disease. If patient recruited ≥6months after initial BAPE diagnosis, then visit 1 and 2 can be combined at day 0.*

5 Scientific Background and Study Rationale

5.1 Scientific Background

5.1.1 Introduction

MPM is an invasive thoracic malignancy associated with prior asbestos exposure. It typically develops 30-50 years after inhalation of asbestos fibres and frequently presents with breathlessness resulting from a pleural effusion. Median survival is poor at 9.5 months, and is principally determined by performance status and histological subtype. (10) Despite recent improvement in the resources available for the management of MPM, the disease remains universally fatal and there has only been a modest improvement in survival rates. (11)

5.1.2 Diagnosis of Incident MPM

Contrast enhanced computed tomography (CT) remains the key radiological investigation for suspected pleural malignancy (PM), including MPM. (12) Features of pleural malignancy visible on CT include more than one centimetre of pleural thickening, nodular or mediastinal pleural thickening, inter-lobar fissural modularity and infiltration of the chest wall or diaphragm (13, 14). However, results from a recent study suggested that almost half of patients with an eventual diagnosis of pleural malignancy have a benign CT. (15) Therefore, a benign CT report should not be used alone in confirming a non-malignant diagnosis.

The diagnostic yield of fluid cytology in malignant pleural effusion is approximately 60%, varying by tumour type (12). However, this is significantly lower in MPM, due to the bland cytological appearance of MPM cells, making it difficult to differentiate MPM from benign reactive mesothelial proliferation. This is reflected in the recommendations made in the recent BTS guidelines for MPM, which recommends histological confirmation of all cases. (16)

Local Anaesthetic Thoracoscopy (LAT) allows direct visualisation of abnormal areas of pleura, multiple biopsies to be taken and provision of definitive pleural effusion management, e.g. pleurodesis, within a single procedure. LAT is well-tolerated and can be performed as a day-case. It offers high diagnostic sensitivity (MPM sensitivity 92.6%, specificity 100% n=1369 cases) and is associated with a low complication rate (0% mortality in over 2000 diagnostic LAT cases across 28 studies and a 1.8% major complication rate in over 4500 LAT cases across 47 studies). (17)

Thoracic ultrasound (TUS) is necessary to assess the pleural space characteristics prior to LAT. During respiration, the parietal pleural slides on the visceral pleural, producing the ‘sliding sign’. This would not be present if there was pleural adherence, previous pneumothorax or previous pleurodesis. Therefore, the presence of the ‘sliding sign’ can be used to assess LAT feasibility. TUS can also identify potential challenges to thoracoscopy such as pleural thickening and septation. (8) In cases where LAT is not feasible because either the patient is frail, pleural fluid is heavily located, or where the lung is adherent to the chest wall, TUS-directed cutting pleural biopsy should be considered as an alternative (9).

5.1.3 Benign Asbestos-related Pleural Effusion

Patients with suspected pleural malignancy are frequently found to have non-specific pleuritis/pleural fibrosis at LAT or image guided biopsy. When associated with prior asbestos exposure, these patients are given the label of 'Benign Asbestos-related Pleural Effusion (BAPE)'. A retrospective, single-centre study of 142 LAT patients reported BAPE in 31% of patients, of whom12% (95% CI 4.5% - 26.4%) subsequently developed MPM over 2 years of follow-up (2). Consequently, patients with BAPE are routinely followed up in pleural clinics and repeat biopsies pursued if pleural effusion recurs or there are other indicators of MPM.

Benign asbestos-related pleural effusion (BAPE) is one cause of non-specific pleuritis. Although this syndrome was initially described in 1964 (18), the true nature and outcome of these patients has been poorly studied. In particular, it is not clear whether BAPE is a genuine precursor of MPM in some patients, or simply a reflection of false negative biopsies in a minority of patients with thoracoscopically occult MPM. Alternatively, BAPE could reflect an unrelated inflammatory episode that promotes MPM via the pro-angiogenic and immunosuppressive factors known to exist within pleural effusion (19). Whatever the mechanism, BAPE constitutes a unique cohort in which to study early MPM biology.

5.2 Rationale for the Meso-ORIGINS Feasibility Study

In a future study, called Meso-ORIGINS, we aim to define the key biological events that drive or permit evolution of MPM by recruiting a large population of patients with BAPE. According to the optimal (but most invasive) Meso-ORIGINS design, the study will utilise sequential LAT biopsies acquired over 2-year period preceding the development of MPM. These will facilitate unprecedented surveillance of the driving (oncological) and/or permissive (immunological) events involved in the development of MPM. The Meso-ORIGINS feasibility study will address important areas of uncertainty with regard to the current Meso-ORIGINS design, particularly the feasibility of the currently proposed surveillance protocol (involving LAT), patient acceptability and the sample size required (currently estimated at 850). Patient acceptance of alternative strategies for surveillance will be explored including imaging, blood tests for biomarkers (3, 4) and breath tests (5, 6, 7).

In a prospective element, the Meso-ORIGINS feasibility study will determine the technical feasibility of LAT based on TUS measurements. A Patient Acceptability Questionnaire will be used to determine patients' views on this and a range of less invasive alternative surveillance strategies. A retrospective cohort study using LAT/VAT and image guided pleural biopsy databases at each site will determine more precisely the subsequent incidence of MPM in patients diagnosed with BAPE. If the true MPM rate is lower than the 12% previously reported (2) this would mandate a larger, potentially unfeasible sample size

6 Patient Selection

6.1 Inclusion Criteria

All study participants involved in either the Prospective Feasibility Study or the Retrospective Cohort Study will be subject to the following inclusion criteria:

- History of asbestos exposure *or* compatible radiology, e.g., pleural plaques
- CT imaging compatible with BAPE (which must include pleural effusion) or compatible histological diagnosis at biopsy including any of the following: benign fibrinous pleurisy, non-specific pleuritis or atypical mesothelial proliferation

NB Histological confirmation is required for the Retrospective Cohort Study

Patients recruited to the Prospective Feasibility Study must also meet the following additional inclusion criteria:

- Informed written consent
- Expected prognosis ≥ 6 months

6.2 Exclusion Criteria

All study participants involved in either the Prospective Feasibility Study or the Retrospective Cohort Study will be subject to the following exclusion criteria:

- Histological diagnosis of MPM or any secondary pleural malignancy
- Diagnosis of pleural infection, empyema or granulomatous pleuritis

In addition, potential cases identified for the Retrospective Cohort Study must also be assessed against the following **additional exclusion criterion:**

- < 2 years follow-up completed at the point of enrolment

6.3 Prospective Feasibility Study Screening and Recruitment

Patients potentially meeting the eligibility criteria will be identified at routine outpatient clinics, lung or pleural MDTs and/or during inpatient reviews or LAT sessions. A medically qualified investigator will review inclusion and exclusion criteria and complete the eligibility assessment form. Patients that meet all inclusion criteria and who do not have obvious exclusion criteria will be recorded in a screening log. Eligible patients will be provided with a Patient Information Sheet (PIS) and invited to participate on a consecutive basis. This activity will occur at routine outpatient clinic. All patients will be given sufficient time to consider study participation (in their own judgment); this need not be 24 hours or greater.

If patients are agreeable to trial involvement, a member of the research team will identify a suitable opportunity to address any questions and to seek written informed consent prior to study enrolment. Provision of the study PIS, study discussion, consent and enrolment can all occur on the first study visit (see Section 7).

6.4 Retrospective Cohort Study Case Identification

Electronic databases will be used to identify cases meeting the study eligibility criteria. Existing databases in the trial centres involved contain data on approx. 1000 patients that have undergone LAT. These database should contain approx. 300 cases of BAPE based on previously published BAPE incidence of 30% in this population (2). Existing databases from VATS and image guided biopsy cases will also be used.

Cases can be entered throughout the period that the study is open. This includes cases diagnosed with BAPE with less than 2 years follow-up at the point the study opens, so long as 2 years follow-up has concluded by the time they are enrolled. The retrospective study will end after 12 months from opening and therefore patients who had a diagnosis of BAPE following LAT on or before 31/11/17 could be recruited.

6.5 Co-enrolment Guidelines

There will be no restriction on co-enrolment in other studies. However, the lead centre must be informed of such activity as soon as possible.

6.6 Bias Reduction

In the retrospective study there is potential for recall and omission bias in data collection. We expect that this will be minimal as each centre that will be collecting data will have prospective databases where all LAT/VATS/image guided biopsies are recorded. In the prospective feasibility study there will be consecutive multicentre recruitment which will improve generalisation to a UK population. This is important as the data gathered will ultimately be used in the design of a future larger study.

7 Prospective Feasibility Study Procedures and Assessments

7.1 Pre-enrolment

Patients will be identified for potential study participation at routine outpatient clinics, lung or pleural MDTs, inpatient reviews or LAT sessions.

7.2 Eligibility Assessment and Consent

Patients identified as meeting the initial eligibility criteria will be approached by a member of the research team at their first clinic appointment following diagnosis of BAPE (after CT or biopsy if indicated) and provided with a study PIS –‘Visit 1’. Visit 1

can also be completed during an inpatient stay, if required. Patients with a radiological diagnosis of BAPE can also be recruited from clinics at any stage in their follow up if they meet inclusion/exclusion criteria.

Eligibility will be documented by a medially qualified member of the team prior to registration and written consent being sought. Sufficient time will be given for the patient to consider involvement and to have any questions relating to the study answered. If the patient would like more time to consider their involvement, a member of the research team will contact discuss this at a later date. Screened patients will be recorded as on a Screening Log.

7.3 Registration

Patients cannot be screened or registered to the trial until the site has been activated to begin recruitment. All study participants should be registered after Eligibility Assessment. Registration requires an email to be sent to the following address.

gg-uhb.mesoorigins@nhs.net

A study number will be sent by return email to the site within the same working day. The patient is considered to be registered once a registration email has been sent.

7.4 Study Visits

7.4.1 Visit 1

Visit 1 activities will occur at clinic appointment following biopsy or at any stage in follow up of radiological diagnosis of BAPE cases.

Visit 1 activities will include:

- Provision of Patient Information Sheet
- Confirmation of eligibility by a medically qualified team member
- Documentation of informed written consent (medically qualified team member not required)
- Registration of patient by email (gg-uhb.mesoorigins@nhs.net)
- Completion of Baseline CRF, which will include the following data:

Demographics	Age*, Gender
Asbestos Exposure History	Occupation Period of employment Job Type & Code** Indirect exposure details
CT Findings*	Benign or Malignant Features • Based on previously reported criteria (9,15) Calcified Pleural plaques • Present or Not Present
CXR appearance*	Effusion Laterality

	Effusion Size: • Small effusion (<50% thorax) • Large effusion (≥50% thorax)
LAT details (if applicable)	Were adequate views obtained? Which surfaces were abnormal? What was the nature of the abnormality/ies? • Smooth • Macro-nodular • Micro-nodular Number of biopsies Did the lung prove non-expansile (based on BTS criteria (≥50% re-apposition) (19) Did the subject have pleurodesis? Did the subject have an IPC placed? Histology, Cytology, Pleural Fluid Chemistry Results

*at presentation

***Job type options and codes available in CRF*

7.4.2 Visit 2

Visit 2 should coincide with a clinic visit approximately 6 months after Visit 1. However, Visit 2 activities can be completed 2 weeks earlier or later than 6 months following biopsy if the patient presents with symptomatic recurrence of pleural effusion or any other manifestation of progressive ipsilateral pleural disease (in the judgment of the site PI). If patient recruited ≥6months after initial BAPE diagnosis then visit 1 and 2 can be combined on Visit 1.

Visit 2 activities will include:

- History and examination
- Completion of Patient Acceptability Questionnaire
- Thoracic Ultrasound for assessment of LAT Feasibility based on thoracic ultrasound markers (8). Technical feasibility of LAT will be defined as either:
    - sufficient pleural fluid to allow safe LAT access *or*
    - sufficient lung-sliding to allow pneumothorax induction prior to LAT
- Recording of any new pleural diagnosis and/or the results of any further imaging or sampling tests

7. 5 Trial Images

All CXR and CT images relating to trial participation will be securely stored on NHS PACS systems in line with routine clinical practice.

7.6 End of Trial

Trial recruitment will terminate after 54 patients have been recruited, after 27 patients have been met the primary end-point regarding feasibility, or 12 months after the study opens, whichever is soonest. The trial will end once the final patient recruited has completed their 2-6 month follow up visit (Visit 2).

7.7 Schedule of Assessments

Visit Number	**1**	**2**
Approximate timing	Day 0 (Recruitment)	6 months* (+/-2weeks)
Clinical Activity		
Clinical review	x	x
Chest Radiograph	x	x
Thoracic ultrasound	x	x
Study Activity		
Review Eligibility Criteria** and complete eligibility assessment form	x	
Introduce study if eligible	x	
Provide with PIS	x	
Opportunity for discussion	x	
Informed written consent	x†	
Register patient with CTU by email	x†	
Complete Baseline CRF	x†	
Complete Follow-up CRF, including technical feasibility of LAT based on Ultrasound findings		x
Complete Patient Acceptability Questionnaire		x

** Visit 2 can occur as early as 2 month following date of biopsy if patient presents with symptomatic recurrence of pleural effusion or any other manifestation of progressive ipsilateral pleural disease (in the judgment of the site PI). If patient recruited ≥6months after initial BAPE diagnosis then visit 1 and 2 can be combined at day 0.*

*** Eligibility for the study must be confirmed by a medically qualified member of the research team. Consent may be documented by a non-medically qualified team member.*

† *If the patient wishes more time to consider participation in the study, these activities may occur at a subsequent research visit arranged by a member of the research team.*

8 Retrospective Study Data Collection and Recording

The following data will be recorded retrospectively for all eligible patients using LAT/VAT/image guided biopsy databases and electronic health records at the study centres. A data collection form (*.xls*) will be provided, including pre-populated study IDs. All data will be recorded in a linked anonymised format.

The date of BAPE diagnosis will be recorded. This is defined as the date on the pathology report describing features of BAPE that meet they eligibility criteria as explained in section 6.

Imaging, pleural fluid and blood results should be recorded at first presentation.

Cases can be entered throughout the period that the study is open. This includes cases diagnosed with BAPE with less than 2 years follow-up at the point the study opens, so long as 2 years follow-up has concluded by the time they are enrolled.

Demographics	Age*, Gender
Asbestos Exposure History	Occupational or environmental Nature of Occupation
CT Findings*	Benign or Malignant Features • Based on previously reported criteria (5,11) Calcified Pleural plaques • Present or Not Present
CXR appearance*	Effusion Laterality Effusion Size: • Small effusion (<50% thorax) • Large effusion (≥50% thorax)
Blood Tests*	Haemoglobin Neutrophils Lymphocytes Platelets CRP Albumin LDH Total Protein

Pleural Fluid	Total protein Albumin LDH Glucose Colour Cytology
LAT/VATS Findings	Date index procedure performed Were adequate views obtained? Which surfaces were abnormal? What was the nature of the abnormality/ies? • Smooth • Macro-nodular • Micro-nodular Number of biopsies Did the lung prove non-expansile (based on BTS criteria (≥50% re-apposition) (20) Did the subject have pleurodesis? Did the subject have an IPC placed? Histology, Cytology, Pleural Fluid Chemistry Results
Follow-up Data	Record any new pleural diagnosis since LAT/VATS Record whether MPM diagnoses within 2 years of index LAT/VATS date

**at presentation*

9 Patient Withdrawal

Patients will be withdrawn from the study if any of the following occur:

- Patient withdrawal of consent
- Clinical opinion of the doctor that the patient should no longer continue in the study

Patients can withdraw their consent for ongoing participation in the study at any point. If this occurs:

- Withdrawal of consent will be clearly documented, along with the level of consent withdrawal and the reason (if the patient has given any)
- A consent withdrawal notification form will be completed.

10 Statistical Considerations

10.1 Sample Size

10.1.1 Prospective Feasibility Study

Each centre performs 30-50 LATs/year (total 120-200/year). Based on a historical incidence of BAPE in 30% in LAT cases (2) we expect there will be 40-60 patients available. The estimated sample size is 54 patients over 12 months, in whom we predict the study will be feasible in a maximum of 50% (n=27).

10.1.2 Retrospective Cohort Study

The target sample size is 300. Existing databases in Glasgow, Bristol, Manchester & Oxford contain data on approx. 1000 patients. Based on a 'BAPE' incidence of 30% (2) in LAT cases, this should be feasible and would be more than double the size of the previous study (2) on which the Meso-ORIGINS sample size estimate is based.

10.2 Statistical Analysis Plan

10.2.1 Prospective Feasibility Study

Results will be reported using simple descriptive statistics. The **Primary Endpoint** shall be met if repeat LAT for research purposes is acceptable to the patient at Visit 2 *and* LAT is technically feasible at Visit 2.

10.2.2 Retrospective Cohort Study

Results will be reported using simple descriptive statistics. The **primary end-point** shall be the rate of MPM transition. This will be calculated by dividing the number of eligible patients diagnosed with MPM within 2 years of the index diagnosis of BAPE by the total number of eligible patients. The **secondary end-point** shall be based on the content of a logistic regression model for MPM transition generated using baseline data as candidate predictors.

11 Safety Reporting

Adverse events are not expected in this study since the only study activities involved recording of routinely performed clinical data and completion of a questionnaire. Safety reporting is therefore not required.

12 Compliance, Audit and Protocol Deviations

12.1 Good Clinical Practice

This study will be conducted in accordance with the protocol, the Sponsor's standard operating procedures, national regulatory requirements, provisions of the relevant ethics committees and Good Clinical Practice (GCP) principles.

12.2 Audits

The study may be subject to audit by NHS Greater Glasgow and Clyde under their remit as Sponsor.

12.3 Protocol Deviation Reporting

A protocol deviation is any departure from the approved protocol. All deviations will be recorded and reported to the sponsor. The sponsor will not authorize prospective protocol deviations/waivers, unless the deviation is necessary to eliminate and immediate hazard.

13 Data Handing

Data generated by the study will be stored in a linked anonymised fashion in a password-protected computer at each site.

13.1 Case Report Forms

Paper case report forms (CRFs) will be provided to each site. Entries to the CRFs will be made in black ballpoint pen and must be legible. Any errors must be crossed out with a single stroke, the correction inserted and the change initialed and dated by the Investigator. Correction fluid must not be used. All data submitted on CRFs must be verifiable in the source documentation and any discrepancies must be recorded and explained.

Trial sites should keep a copy of all completed CRFs. The original CRFs should be returned to the Pleural Disease Unit, Queen Elizabeth University Hospital for data entry and computation of relevant end-points and ultimately, statistical analysis.

13.2 Data Storage and Archiving

CRFs from the trial will be stored in line with current regulatory requirements. Other essential documents, including source data, consent forms, and regulatory documentation, will be archived by the Investigator, in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection as required.

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