


BMJ Open Results of the Meso-ORIGINS feasibility study regarding collection of matched benign-mesothelioma tissue pairs by longitudinal surveillance

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ABSTRACT

Objectives To assess key elements of the design for Meso-ORIGINS (Mesothelioma Observational study of Risk prediction and Generation of paired benign-meso tissue samples, Including a Nested MRI Substudy), an ambitious, UK-wide, prospective study that will collect ≥ 63 matched benign-mesothelioma tissue pairs through longitudinal surveillance and repeat biopsy of patients with asbestos-associated pleural inflammation (AAPI).

Design A multicentre, mixed-methods feasibility study, comprising a prospective observational element, evaluating recruitment feasibility, technical feasibility of repeat local anaesthetic thoracoscopy (LAT) and patient acceptability, and a retrospective cohort study focused on AAPI-mesothelioma evolution rate, informing sample size.

Setting 4 UK pleural disease centres (February 2019–January 2020).

Participants Patients with AAPI (history or typical imaging plus appropriate pleural histology) were eligible for both elements. In August 2019, eligibility for the prospective element was broadened, including addition of radiological AAPI for technical feasibility and patient acceptability endpoints only. Retrospective cases required ≥ 2 years follow-up.

Outcome measures A prospective recruitment target was set a priori at 27 histological AAPI cases (or 14 in any 6 months). Technical feasibility and patient acceptability were determined at 6-month follow-up by thoracic ultrasound surrogates and questionnaires, respectively. Retrospective malignant pleural mesothelioma evolution rate was defined by proportion (95% CI). Baseline predictors of evolution were identified using logistic regression.

Results 296 patients with AAPI (39 prospective, 257 retrospective) were recruited/selected. 21/39 prospective recruits were histologically diagnosed (target $n=27$). Repeat LAT was technically feasible and acceptable in 13/28 (46%) and 24/36 (67%) cases with complete follow-up data. Mesothelioma evolution was confirmed histologically in 36/257 retrospective cases (14% (95% CI 10.3% to 18.8%)) and associated with malignant CT features (OR 4.78 (95% CI 2.36 to 9.86)) and age (OR 1.06 (95% CI 1.02 to 1.12)).

Conclusions Our initial eligibility criteria were too narrow. Meso-ORIGINS will recruit a broader cohort, including

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ We performed a mixed-methods feasibility study, with dedicated prospective and retrospective elements assessing key elements of the Meso-ORIGINS (Mesothelioma Observational study of Risk prediction and Generation of paired benign-meso tissue samples, Including a Nested MRI Substudy) study design.
- ⇒ Meso-ORIGINS is a prospective multicentre study, which will collect matched benign-mesothelioma tissue pairs through longitudinal surveillance of patients with asbestos-associated pleural inflammation and repeat biopsy, if clinically indicated.
- ⇒ The prospective element deployed an initial set of eligibility criteria and evaluated the technical feasibility and the acceptability of the surveillance and rebiopsy protocol, including local anaesthetic thoracoscopy.
- ⇒ There is potential for recall bias in the retrospective cohort study, although each participating centre maintains a prospective database, which should minimise this.

prevalent cases, any biopsy type and patients with malignant CT features. A range of rebiopsy techniques will be allowed, accounting for technical and patient factors. The sample size has been reduced to 500.

Trial registration number ISRCTN12840870.

BACKGROUND

Malignant pleural mesothelioma (MPM) is an aggressive cancer caused by prior asbestos exposure. Despite recent positive clinical trials,^{1 2} most new drug therapies for MPM have failed, with only 6% reaching phase III in a recent survey.³ The outlook for patients with MPM therefore remains poor, with a median survival of less than a year.⁴ The development of new drugs for MPM poses several unique challenges. The MPM tumour genome is dominated by tumour suppressor



loss, with few protein-alternating mutations in obviously druggable oncogenes.^{5 6} MPM is also typically associated with high tumour burden, even at the earliest detectable stage of disease,⁷ probably reflecting the voluminous size of the pleural cavity in which it develops. A better understanding of the processes that drive or permit evolution of MPM is required for development of more effective therapies. This is the focus of the PREDICT-Meso (PRE-malignant Drivers Combined with Target-drug validation in Mesothelioma) International Accelerator, funded by Cancer Research UK (CRUK)/Fundación Científica de la Asociación Española Contra el Cáncer (FC AECC) and Fondazione AIRC per la Ricerca sul Cancro (AIRC).

PREDICT-Meso seeks to take advantage of a unique window of opportunity presented by the disease course of MPM, which typically develops 30–50 years after initial inhalation of asbestos fibres. To date, investigators have been unable to use this latent period to collect human tissue samples before and after MPM develops for the purpose of target identification, drug discovery and validation. However, several recent small studies have shown that in some patients, MPM may be preceded by an episode of pleural effusion and apparently benign inflammation, which requires clinical follow-up because of a risk of MPM evolution over the following years. An often-quoted example of this risk was reported by Davies *et al*, who found that 12% (95% CI 5% to 26%) patients with ‘non-specific pleuritis’ at local anaesthetic thoracoscopy (LAT) developed MPM within 2 years.⁸ It is not clear whether this observation is a genuine precursor of MPM or simply reflects false-negative biopsies in patients with thoroscopically occult MPM. However, the former hypothesis is certainly plausible, with a preceding inflammatory trigger promoting MPM via pro-angiogenic and immunosuppressive factors known to exist within pleural effusions.^{9 10} Whatever the truth of the presentation, this sequence of events provides a unique opportunity in which to study early MPM biology by creating rare inpatient tissue pairs combining preceding pleural inflammation and subsequent invasive MPM. Collection of this material will be performed in the Meso-ORIGINS (Mesothelioma Observational study of RiSk prediction and Generation of paired benign-meso tissue samples, Including a Nested MRI Substudy), which is embedded in the PREDICT-Meso programme (see www.predict-meso.com). The tissue collected will be used by an international team of preclinical scientists for multiomic target identification and for development of a suite of preclinical models and high-throughput drug screening. Tissue and other samples (including blood, exhaled breath and imaging) will be banked and used for parallel risk prediction studies designed to identify patients who could reasonably be recruited to future early intervention trials.

The primary objective of Meso-ORIGINS is to create a prospective, longitudinal cohort of patients with asbestos-associated pleural inflammation (AAPI), of whom at least 63 patients will develop MPM over the 2-year study follow-up. A minimum of 63 matched benign-MPM

tissue pairs are needed to adequately power the downstream bioinformatics and drug development pipelines. The current feasibility study was performed to address key areas of uncertainty regarding the Meso-ORIGINS design, including the minimum sample size of patients with AAPI needed to generate 63 benign-MPM evolutions within 2 years, recruitment feasibility of the initial sample size estimate (n=590, based on the 12% (95% CI 5% to 26%)) rate reported by Davies *et al*,⁸ and the technical feasibility and acceptability to patients of the proposed 2-year surveillance +/- repeat biopsy strategy. The ‘ideal’ protocol from a scientific perspective would involve initial and repeat biopsies using LAT, since this allows complete visual inspection of the entire pleural space and collection of numerous full-thickness pleural biopsies. However, given the exploratory nature of the design, it was not clear at the point of conception, whether reliance on LAT biopsies for eligibility would unduly restrict recruitment. It was also not clear whether it would be technically feasible to perform repeat LAT after fluid drainage, given the potential for auto-pleurodesis or pleural space septation. Furthermore, we were unsure whether patients would find it acceptable to consent to repeat biopsy by LAT (or any other invasive method). It was also considered essential to improve the precision of the sample size estimate for the main study, since the wide CIs surrounding the MPM evolution rate point estimate reported by Davies *et al* (12% (95% CI 5% to 26%))⁸ meant the true sample size needed could be as high as 1260 (if the true MPM evolution rate was 5%), making the main study unfeasible. The Meso-ORIGINS feasibility study was therefore a mixed-methods study incorporating a prospective observational cohort study focused on recruitment feasibility, technical feasibility and patient acceptability, plus a retrospective cohort study focused on improved precision of the sample size estimate.

METHODS

Design and setting

The overall design involved a prospective observational study and a retrospective cohort study. Both elements were multicentre and recruited or selected, respectively, patients with AAPI from one of four UK pleural disease centres: (1) Queen Elizabeth University Hospital, Glasgow; (2) Southmead Hospital, Bristol; (3) Churchill Hospital, Oxford and (4) Wythenshawe Hospital, Manchester. This study was sponsored by NHS Greater Glasgow and Clyde and recruited for 12 months (February 2019–January 2020). The protocol was approved by NHS Health Research Authority South Central-Hampshire B Research Ethics Committee (reference 18/SC/0617) and was registered (ISRCTN12840870).

Objectives and endpoints

Prospective observational study

The primary objective was to determine whether it would be possible to recruit sufficient numbers of eligible

patients within the time available to the main study (41 months). This was initially based on eligibility criteria and a surveillance and rebiopsy protocol that required LAT sampling at both timepoints. However, these strict criteria were broadened after 6 months by protocol amendment (see the Protocol amendments section). The primary endpoint was recruitment rate. Recruitment feasibility was defined a priori as recruitment of 27 eligible participants over 12 months (or 14 patients during any 6-month period). This threshold was based on planned delivery of the main study in 25 sites, which would translate into 590 cases over 41 months (27 patients being equivalent to 2.25 patients/month over 4 sites). The study team has recently recruited 747 patients from 23 UK sites over 3 years to a similar study¹¹ and considered this size of study deliverable.

The primary objective also included assessment of the technical feasibility of repeat LAT. However, it was not considered ethical to directly test this until the study was proven deliverable. This was therefore assessed indirectly, using established sonographic markers¹² (see online supplemental section 1), and is reported separately to recruitment rate, given the broader eligibility criteria deployed postamendment.

The secondary objective was to explore patient acceptability, including reasons for patients declining repeat LAT, and the acceptability of alternative resampling methods, including pleural fluid aspiration, pleural needle biopsies, imaging, blood and breath tests. The secondary endpoint was the outcome of a simple unvalidated patient acceptability questionnaire (see online supplemental section 2).

Retrospective cohort study

The primary objective was to determine the rate of MPM evolution more precisely than previous smaller studies, thereby improving the precision of the sample size estimate for Meso-ORIGINS. The primary endpoint was the MPM evolution rate, and its associated 95% CI. This was defined as the number of eligible patients diagnosed with MPM within 2 years of the index diagnosis of AAPI divided by the total number of patients with AAPI. The secondary objective was to identify baseline predictors of MPM evolution; the intention being to use any features identified to refine the eligibility criteria for the main study and maximise the MPM evolution rate therein. The secondary endpoint was the output of a logistic regression model based on baseline data.

Eligibility

Patients with AAPI were sought for both studies, using similar eligibility criteria, with appropriate adjustments to address the different objectives.

Prospective observational study

Inclusion criteria

Participants were subject to all of the following: (1) history of asbestos exposure or compatible radiology,

for example, pleural plaques; (2) histological findings compatible with AAPI on any previous pleural biopsy (eg, benign fibrinous pleurisy, non-specific pleuritis, atypical mesothelial proliferation) or a confident radiological diagnosis based on CT imaging (must include pleural effusion +/- pleural thickening or plaques) and exclusion of other causes (eg, following pleural fluid aspiration); (3) informed written consent and (4) prognosis ≥ 6 months. Note, criterion (2) was broadened from an initial definition that allowed only histological diagnoses made by LAT after feedback from sites (see the Protocol amendments section).

Exclusion criteria

Participants were excluded if any of the following criteria were met: (1) histological or cytological diagnosis of MPM or any secondary pleural malignancy and (2) diagnosis of pleural infection, empyema or granulomatous pleuritis.

Retrospective cohort study

Inclusion criteria

Potential cases were subject to all the following: (1) history of asbestos exposure or compatible radiology, for example, pleural plaques and (2) compatible histological findings on any previous pleural biopsy (eg, benign fibrinous pleurisy, non-specific pleuritis, atypical mesothelial proliferation).

Exclusion criteria

Cases were excluded if any of the following were met: (1) < 2 years follow-up at eligibility assessment; (2) histological or cytological diagnosis of MPM or any secondary pleural malignancy and (3) diagnosis of pleural infection, empyema or granulomatous pleuritis.

Screening, consent and study interventions

Prospective observational study

Study activities are summarised in the flow chart in the online supplement (online supplemental section 3). Eligibility was assessed during outpatient clinic attendances or inpatient encounters. Following provision of a patient information sheet and informed written consent, baseline data were recorded at visit 1. This included asbestos exposure history, demographics, CT and chest radiograph (CXR) findings. CT findings were codified into benign or malignant, based on previously reported descriptors^{13 14} and by the presence of pleural plaques. CXR was used to classify effusion size as small or large ($< 50\%$ / $\geq 50\%$ hemithorax opacification). A second study visit was completed 6 months later but could be completed at any time during the 6-month follow-up period if the patient presented with progressive ipsilateral pleural disease suggestive of possible MPM evolution, which was recorded if it occurred.

Following a single protocol amendment 6 months into recruitment, visit 2 could also be combined with visit 1 if the diagnosis of AAPI had been made ≥ 6 months prior to enrolment (since this amendment allowed recruitment of prevalent not just incident cases, see the Protocol

amendments section). At visit 2, a thoracic ultrasound (TUS) scan was performed to assess the technical feasibility of repeat LAT according to a standardised protocol (see online supplemental section 1). Established sonographic markers,¹² including the presence of sufficient fluid, the presence of septations and evidence of 'lung sliding', were recorded and used to classify LAT feasibility, in addition to the feasibility of a TUS-guided needle biopsy (TUS-GNB), based on visualisation of suitable and accessible target lesions. At visit 2, patients were also asked to complete a simple, unvalidated patient acceptability questionnaire (see online supplemental section 2) regarding repeat sampling options, including breath tests, blood tests, pleural fluid sampling and LAT.

Retrospective cohort study

Potentially eligible cases were identified from existing databases at each site, supplemented by pathology department and electronic health records. Baseline data corresponding to the date of the index AAPI diagnosis were recorded, matching those collected in the prospective study. These were supplemented by baseline blood results, including haemoglobin, neutrophil, lymphocyte and platelet counts, C reactive protein, albumin, lactate dehydrogenase (LDH) and total protein, and baseline pleural fluid measurements, including total protein, LDH, glucose, macroscopic appearance (eg, blood-stained) and cytology.

Sample size and statistical analyses

For the prospective study, a formal sample size calculation was not possible. We planned to recruit up to 54 patients over 12 months, of whom we expected at least 50% (n=27) to be meet the primary endpoint. Each of the four study centres performs 30–50 LATs/year (total 120–200/year), generating a potentially recruitable cohort of 40–60 patients, based on a historical incidence of non-specific pleuritis in 30% of LAT cases.⁸ Simple descriptive statistics were used to report the primary and secondary endpoints. Baseline data are reported as mean (SD) or median (IQR), depending on distribution, or percentage (%).

The maximum sample size available for the retrospective cohort study was considered to be 300, based on a historical incidence of non-specific pleuritis in 30% of LAT cases⁸ and an estimated total of 1000 cases in the LAT databases at the four study centres. Assuming a similar MPM evolution rate as previously reported by Davies *et al* (12% (95% CI 5% to 26%), which was based on 5 MPM evolutions in 42 AAPI patients),⁸ we projected 36 evolutions in the estimated 300 AAPI cases available, with an associated 95% CI of 9% to 16%. The increased precision in this estimate (95% CI of 21% previously⁸ vs 7% here) was deemed acceptable for the primary endpoint of the retrospective study. It was acknowledged that smaller numbers of AAPI cases in the retrospective study would proportionately reduce the precision achieved. The primary endpoint of the retrospective study is reported

as a proportion with associated 95% CI computed by the modified Wald method.¹⁵ Minimum samples sizes for the subsequent main Meso-ORIGINS study were computed using prediction intervals for binomial data, as proposed by Lu and Jin.¹⁶ The sample size of 300 provided adequate power for the secondary endpoint (a logistic regression model for MPM evolution) to test up to 7 candidate predictor variables, assuming a minimum of 5 events per predictor variable.¹⁷ Baseline features with a univariate $p < 0.05$ were included in multivariate model building, assuming no collinearity was observed. Regression results are reported as OR (95% CI) for MPM evolution. Statistical analyses were performed in GraphPad Prism V.9.1.0 (San Diego, California, USA) and R (V.4.0.0, Vienna, Austria).

Protocol amendments

A single amendment to the prospective study was implemented in August 2019 following review of screening data and site feedback. This broadened eligibility to include histological diagnoses made by any pleural biopsy (previously LAT only) and prevalent cases in clinic follow-up (previously incident cases only). The amendment also allowed recruitment of radiological diagnoses after exclusion of other causes (previously histological only), maximising numbers for the secondary objectives. It was acknowledging that patients without histological confirmation would not contribute to the primary endpoint regarding recruitment rate. Primary endpoint data regarding technical feasibility of repeat LAT based on TUS data are therefore reported separately. This amendment also allowed compression of visits 1 and 2 into a single visit if recruitment occurred ≥ 6 months after diagnosis in prevalent cases.

Patient and public involvement

Input from patients to the final design of Meso-ORIGINS was a key goal of the current study and is reflected in the secondary objectives. All patient facing materials used were reviewed by lay members of the research ethics committee. The Meso-ORIGINS Study Management Group includes a named PPI representative, who is fully involved in study design and delivery. Details of wider PPI activities of the PREDICT-Meso team can be found online (www.predictmeso.com/ppi-and-public-engagement).

RESULTS

Prospective study

Primary objective: recruitment and technical feasibility

Thirty-nine patients were recruited over the 12-month study period (Glasgow (21), Manchester (12), Bristol (5), Oxford (1)). A study flow chart is presented in [figure 1](#). Twenty-one of 39 (54%) recruits had a histological diagnosis, meaning the target of 27 was not achieved, see [figure 2](#) ((a) recruitment rate and (b) rolling 6-month total). Of the histological cases recruited, only 2/21 (9.5%) were diagnosed by surgical thoracoscopy (or

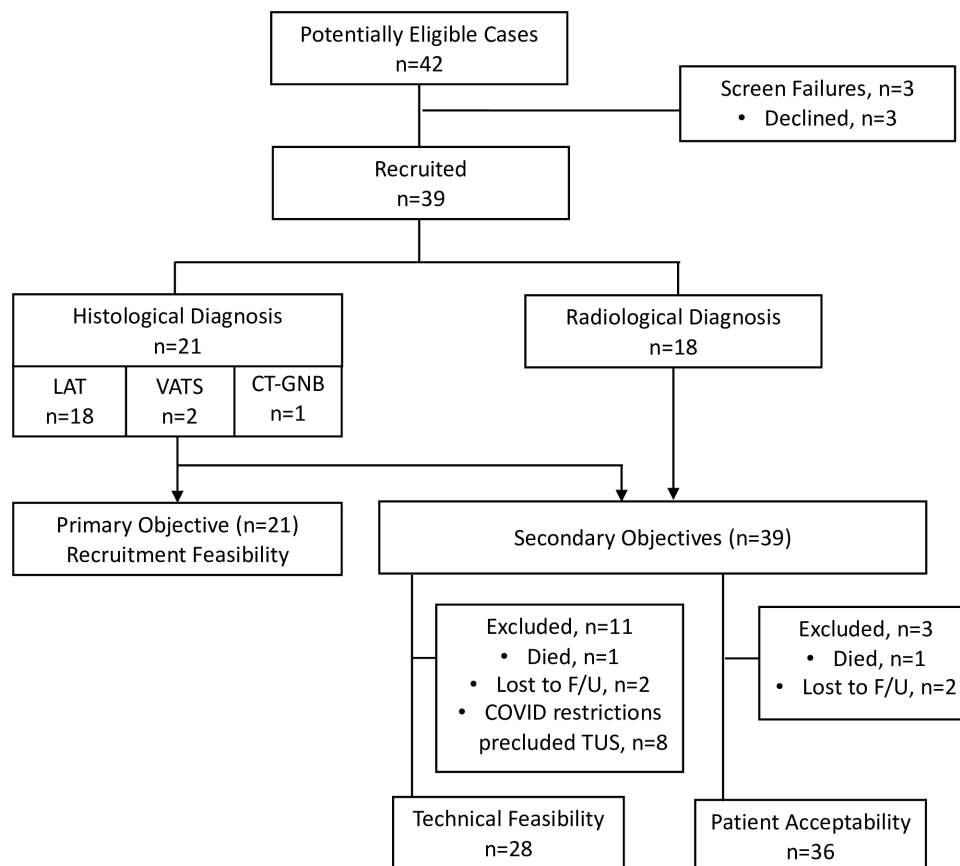


Figure 1 Prospective study flow chart summarising patient recruitment, and numbers of patients completing study activities and reasons for unavailable data. Recruits are separated into those with histological diagnosis, who were eligible to contribute to the primary endpoint and those with radiological diagnosis who were not. Follow-up (F/U) data regarding the technical feasibility of local anaesthetic thoracoscopy (LAT) and patient acceptability were combined from histological and radiological diagnoses for the secondary endpoint analyses. CT-GNB, computed tomography-guided needle biopsy; TUS, thoracic ultrasound; VATS, video-assisted thoracoscopic surgery.

video-assisted thoracoscopic surgery). Baseline characteristics of the recruited population are summarised in [table 1](#). There were no statistically significant differences between baseline features in histological versus radiological diagnoses (see online supplemental section 4).

A complete assessment of LAT technical feasibility could not be completed in 11/39 patients, who could not attend visit 2 due to COVID-19 restrictions, precluding the prerequisite TUS examinations. In the 28/39 cases with TUS data, a pleural effusion was detected in 20/28 (71%) and LAT was technically feasible in 13/28 (46%). A detailed summary of TUS findings can be found in online supplemental section 5. Of the 15/28 non-feasible cases, effusion was observed in 9/15 (60%). Effusions were generally small (median 1 (range 1–3)) rib spaces, and 2/9 cases were severely septated. Lung sliding was absent from 7/9 non-feasible cases with effusions suggesting small, fixed spaces. In the remaining 6/15 non-feasible cases without effusion, sliding was observed in 4/6, at a median of 3.25 (range 2–6) positions. This suggests these spaces might be accessible by pneumothorax induction in centres with appropriate training. TUS-GNB was technically feasible in 3/28 (11%). Therefore, rebiopsy by LAT or TUS-GNB was feasible in 16/28 (57%) cases.

Secondary objective: patient acceptability

Acceptability questionnaires were completed by 36/39 patients (see [figure 1](#)). In 9/36 patients, questionnaires were completed by telephone due to COVID-19 restrictions. Repeat investigation was deemed acceptable by LAT in 24/36 (67%) patients, by needle aspiration in 29/36 (81%), by breath test or CT scan in 35/36 (97%) and by blood test or MRI scan in 36/36 (100%). Image-guided pleural biopsy was not explicitly assessed in this questionnaire, but responses regarding pleural fluid aspiration are taken as a surrogate for this, given their similarity in terms of patient experience and risk.

Post hoc analysis regarding mesothelioma evolution

Mesothelioma was subsequently diagnosed in 4/39 patients recruited to the prospective study (10.3% (95% CI 3.5% to 24.2%)). Repeat sampling was deemed feasible in all four cases and confirmed histologically by CT-guided biopsy in three of four cases. In the fourth case, LAT was planned based on clear radiological progression but not performed due to deteriorating patient fitness.



Figure 2 The recruitment target for the prospective study was 27 patients over 12 months or 14 patients in any 6-month period. Panel (A) shows cumulative recruitment of patients eligible to contribute to the primary endpoint over 12 months (histological diagnoses only). The solid line shows patients recruited using the original eligibility criteria, based around local anaesthetic thoracoscopy biopsies showing asbestos-associated pleural inflammation in incident cases only. The dashed line shows the total number of patients recruited following a single protocol amendment (blue vertical line) which broadened the eligibility to include biopsies of any type and prevalent cases (n=21). The solid line continuing after the protocol amendment shows the number of recruits that would have been achieved if the original criteria had been retained (n=16). Panel (B) summarises the cumulative recruitment over rolling 6-month recruitment periods. The target of 14 recruits in any 6-month period was not achieved. Higher recruitment was observed in periods encompassing the broadened eligibility criteria (August onwards). In several 6-month periods, cumulative recruitment approached the alternative threshold of 14 (see April–September and June–November).

Retrospective study

Primary objective: MPM evolution rate

Flow through the study is summarised in [figure 3](#). Baseline characteristics of the eligible population (n=257) cases are listed in [table 1](#), overleaf. MPM evolution occurred in 42/257 (16% (95% CI 12.3% to 21.4%)) and was confirmed histologically by repeat biopsy or at postmortem in 36/257 (14% (95% CI 10.3% to 18.8%)).

The median time to repeat biopsy was 3.5 months (IQR 2–9.5), excluding cases confirmed postmortem.

Secondary objective: baseline predictors of MPM evolution

Of 11 candidate predictor variables tested by univariate logistic regression, including blood and pleural fluid results, only malignant CT features (OR 4.41 (95% CI 2.22 to 8.9), p<0.0001) and age (OR 1.06 (95% CI 1.02

Table 1 Baseline characteristics of the prospective and retrospective cohorts recruited to the Meso-ORIGINS feasibility study in four UK pleural centres

	Prospective study (n=39)	Retrospective study (n=257)
Age	76 (52–88)	72 (36–90)
Male: gender	39 (100%)	243 (95%)
Asbestos exposed	39 (100%)	257 (100%)
Based on history	39 (100%)	236 (92%)
Based on imaging features only, for example, plaques	0 (0%)	21 (8%)
Pleural effusion characteristics		
Right sided	19 (49%)	126 (49%)
Unilateral	37 (94%)	236 (92%)
<50% of hemithorax on erect chest radiograph	33 (85%)	201 (78%)
CT findings		
Pleural plaques	31 (79%)	167 (65%)
Malignant features	5 (13%)	68 (26%)

Both elements selected patients with asbestos-associated pleural inflammation, and each tested different elements of the proposed Meso-ORIGINS study protocol. Values are reported as median (range) or n (%).

Meso-ORIGINS, Mesothelioma Observational study of Risk prediction and Generation of paired benign-meso tissue samples, Including a Nested MRI Substudy.

to 1.11), $p=0.0055$) were associated with MPM evolution (see table 2). These retained independent associations in subsequent multivariable analyses (age OR 1.06 (95% CI 1.02 to 1.12), $p<0.0001$; malignant CT OR 4.78 (95% CI 2.36 to 9.86), $p<0.0001$).

DISCUSSION

In this multicentre feasibility study, we tested several critical elements of an initial design for Meso-ORIGINS, which will perform biological surveillance of a large cohort of patients with AAPI and collect matched benign-MPM tissue pairs in the minority who evolve into MPM. In Meso-ORIGINS, downstream bioinformatics and preclinical pipelines require at least 63 benign-MPM tissue pairs during a recruitment window of 41 months. Matched benign-benign pairs from 145 patients without MPM evolution are also required for comparative analyses.

In the prospective feasibility study reported here, four UK centres recruited 39 patients in 12 months, following broadening of the original inclusion criteria 6 months into the study. This allowed recruitment of prevalent (not just incident) cases and patients diagnosed using techniques other than LAT. Radiological diagnoses did not contribute to the primary endpoint regarding recruitment rate but added additional cases for the secondary objectives regarding technical feasibility and patient acceptability. Twenty-one of 39 (54%) patients recruited had a histological diagnosis of AABPI at registration, meaning

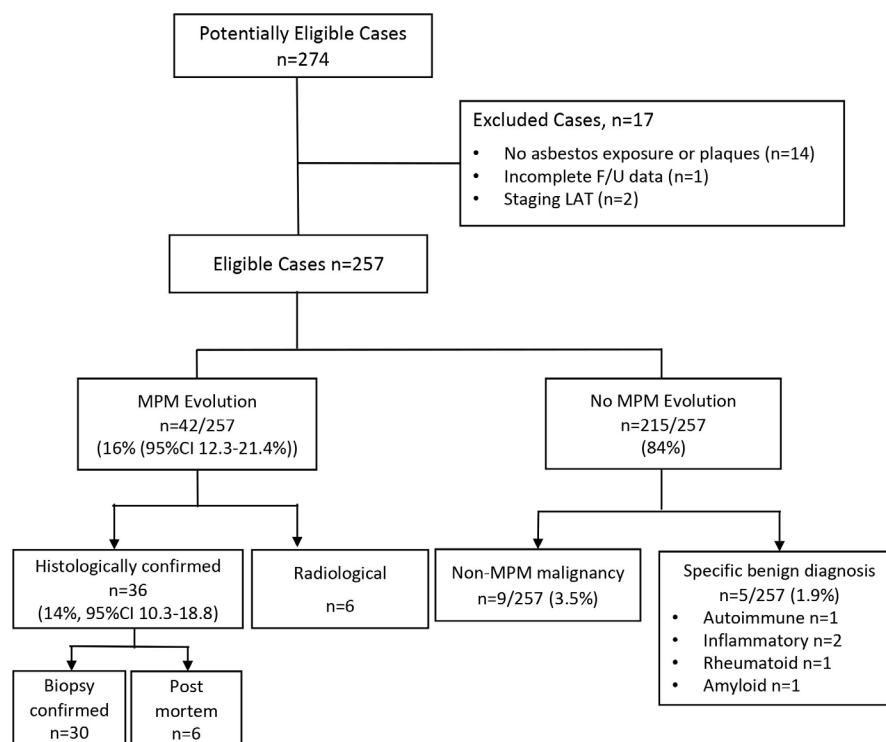


Figure 3 Retrospective study flow chart summarising the selection and screening of historical cases of asbestos-associated pleural inflammation (AAPI) diagnosed at the four study centres. MPM evolution was recorded in a diagnosis of MPM was made within 2 years of the index diagnosis of AAPI. F/U, follow-up; LAT, local anaesthetic thoracoscopy; MPM, malignant pleural mesothelioma.

Table 2 Outcome of logistic regression testing the association between baseline features and subsequent evolution of mesothelioma in patients with benign pleural inflammation recruited to the retrospective study (n=257)

Baseline predictor	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	P value
Age	1.06 (1.01 to 1.11)	0.009	1.06 (1.02 to 1.11)	<0.0001
Pleural plaques on CT	0.89 (0.45 to 1.81)	0.735	–	–
Malignant CT report	4.41 (2.22 to 8.90)	<0.0001	4.78 (2.36 to 9.86)	<0.0001
Asbestos exposure	0.42 (0.16 to 1.25)	0.096	–	–
Large effusion (>50%)	1.85 (0.84 to 3.88)	0.122	–	–
Haemoglobin	1.01 (0.99 to 1.03)	0.369	–	–
Neutrophils	0.91 (0.76 to 1.07)	0.259	–	–
Lymphocytes	1.29 (0.76 to 2.14)	0.339	–	–
Platelets	1.00 (0.99 to 1.01)	0.254	–	–
C reactive protein	0.99 (0.99 to 1.01)	0.864	–	–
Albumin	0.99 (0.93 to 1.02)	0.610	–	–

Variables associated with a univariate p value <0.05 (in bold) were included in subsequent multivariable regression models.

the a priori threshold for recruitment feasibility based on the original design was not met. However, postamendment recruitment was higher than it would have otherwise been (see [figure 2A](#)) and surgically diagnosed cases were notably under-represented. The prospective study also demonstrated that LAT was not technically feasible at follow-up in 54% cases, and highlighted barriers to LAT delivery, which could be overcome in the main study, for example, using pneumothorax induction prior to LAT in cases without effusion. Repeat LAT was acceptable to most, but not all patients (24/36 (67%)), mandating a range of resampling options in the main study. TUS-GNB was feasible in additional 3/28 (11%) patients, and acceptability for this was reassuringly high 29/36 (81%) and near universal for breath tests, CT scans (both 97%), blood tests and MRI scans (both 100%).

In the retrospective element, we observed MPM evolution in 42/257 patients within 2 years of an AAPI diagnosis (16% (95% CI 12.3% to 21.4%)), and confirmed histologically in 36/257 patients (14% (95% CI 10.3% to 18.8%)). The median time to biopsy confirmed MPM evolution was only 3.5 months. Using multivariable logistic regression, age (OR 1.06 (95% CI 1.02 to 1.12)) and particularly malignant CT features (OR 4.78 (95% CI 2.36 to 9.86)) were independently associated with MPM evolution.

Strengths and limitations

We employed a mixed-methods approach, with prospective and retrospective elements specifically testing different elements of the proposed Meso-ORIGINS design. The study centres involved are also representative of future Meso-ORIGINS sites, maximising the generalisability of our results to that study. There is potential for recall bias in the retrospective cohort study, although each participating centre maintains a prospective database which should minimise this. COVID-19 restrictions also meant we were unable to complete face-to-face follow-up visits in

11/39 participants in the prospective study, reducing the volume data available to assess LAT feasibility and patient acceptability.

Implications for the main study design

Eligibility criteria and rebiopsy strategy

The data collected revealed important flaws in the original eligibility criteria, which limited inclusion to LAT-diagnosed incident cases. Although LAT is desirable at baseline and rebiopsy given the number and size of biopsies available,^{18 19} this design would make the study unfeasible. While the a priori recruitment target (n=27) might have been achieved if the broader eligibility criteria have been deployed earlier, further changes will be made for the main study, including greater engagement with surgical thoracoscopy centres.

The prospective study also demonstrated that a range of rebiopsy strategies will be needed in the main study, since LAT is likely to be unfeasible for technical reasons including auto-pleurodesis or extensive fluid loculation, based on TUS surrogates of these events reported in nearly half of the patients reported here. The current study also demonstrated that although all rebiopsy strategies, including LAT, were acceptable to most patients, this was not universal (67% for LAT, 81% for pleural fluid aspiration, which involves a similar experience and risk to TUS-GNB). The main study protocol will therefore include a dedicated screening visit for patients eligible for rebiopsy, which will allow the full range of resampling options to be explored based on their technical feasibility (principally based on TUS appearances for LAT and TUS-GNB) and the individual preferences of the patient and investigator. The options for rebiopsy will include LAT, which will be the preferred option given the number and size of the samples available, TUS-GNB or computed tomography-guided needle biopsy (CT-GNB). CT-GNB was not assessed here but is routinely used in clinical practice. It is expected that the addition of this option

will maximise the numbers in which some form of repeat biopsy can be acquired, since LAT and TUS-GNB were only technically feasible in a total of 16/28 (57%) cases.

Sample size

Based on the histologically confirmed MPM evolution rate reported here (14% (95% CI 10.3% to 18.8%)), the target sample size of the main study has been reduced from 590 to 500. Using prediction intervals (PIs) for binomial data, as proposed by Lu and Jin,¹⁶ 500 AAPI cases will generate 63 (95% PI 41, 89) MPM evolutions, assuming 10% loss to follow-up (ie, 450 cases completing follow-up). Five hundred recruits will also generate 387 (95% PI 361, 409) participants in whom MPM will not evolve within 2 years. Based on the prospective cohort study findings, repeat benign biopsies (by either LAT or TUS-GNB) will be technically feasible in an estimated 228 (95% PI 152, 300) participants in whom MPM does not evolve within 2 years, exceeding the number of benign-no MPM evolution tissue pairs required (n=145), even when the less-than-universal acceptability of repeat biopsies is accounted for.

Conclusion

The current feasibility study has allowed refinement of the eligibility criteria for Meso-ORIGINS and has prompted significant changes to the rebiopsy strategy and sample size estimate. The study, which forms a major part of the PREDICT-Meso International Accelerator, opened to recruitment in June 2022. The material collected Meso-ORIGINS will be used for multiomic characterisation of the biology associated with mesothelioma evolution, development of a range of preclinical models of preinvasive and early-stage disease, and for high-throughput drug screening and target-drug validation. This information will be complementary to expected data emerging from two observational studies in the USA, which are focused exclusively on patients with germline BRCA1 associated protein 1 (BAP1) mutation (NCT03830229 and NCT044310), which is associated with mesothelioma and other cancers.²⁰ Germline BAP1 status will be recorded in all patients recruited to Meso-ORIGINS alongside asbestos exposure histories designed to capture likely fibre type exposure.²¹ The goal of these efforts is development of new, early intervention therapies, ready for human trials. Additional information is available at www.predict-meso.com, including opportunities for collaboration and access tissues and data.

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Patient consent for publication Not applicable.

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Results Of The Meso-ORIGINS Feasibility Study Regarding Collection Of Matched Benign-Mesothelioma Tissue Pairs By Longitudinal Surveillance

ONLINE ONLY SUPPLEMENT: APPENDIX 1

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SECTION 1: THORACIC ULTRASOUND ASSESSEENT OF LAT FEASIBILITY

Introduction to Method


The purpose of this study specific instruction is to provide guidance to researchers involved in the Meso-ORIGINS feasibility study on thoracic ultrasound (TUS) assessment of local anaesthetic thoracoscopy (LAT) feasibility. This assessment is conducted at Visit 2 in all participants. Researchers are required to have attained at least Level 1 RCR TUS competency and to be experienced in LAT. The final judgement regarding the feasibility of LAT and US-guided needle biopsy should be made by the site Principal Investigator, or a suitably experienced delegate.

INSTRUCTIONS

TUS should be performed with patient lying on the unaffected side in the lateral decubitus position. The following information should be recorded on each TUS case report form:

- Patient position
- Is the pleural effusion present or absent?
- If pleural effusion is present, document:
 - size of effusion (in number of rib spaces)
 - the maximum depth of fluid (in centimetres)
 - echogenicity of the effusion (echogenic or non-echogenic)
 - approximate number of septations at site of potential LAT (none, 0-5, 5-10)
- If pleural effusion is absent, document:
 - is lung sliding visible?
 - number of positions lung sliding is demonstrated
 - is there a suitable site for US guided needle biopsy?
- Whether repeat LAT is feasible based on the above information in the opinion of the site principal investigator who would be performing the LAT.

SECTION 2: PATIENT ACCEPTABILITY QUESTIONNAIRE

		Meso-ORIGINS Patient Acceptability Questionnaire	
Meso-Origins Feasibility Study			
INVESTIGATOR:		REGISTRATION DATE: <u>DD</u> / <u>MON</u> / <u>YYYY</u>	
SITE:		PATIENT TRIAL IDENTIFIER:	

The following questions relate to different types of follow up tests and scans that may help us diagnose Mesothelioma at an early stage. We are interested in whether you would have these performed at follow-up clinic visits over the next 2 years. The clinic visits and tests would be every 6 months so you would have them 4 times during this period:

1. WOULD YOU CONSENT TO A BLOOD TEST WHEN YOU COME TO CLINIC ?	
Yes <input type="checkbox"/>	No <input type="checkbox"/> Please give reasons you would not want to have this: If the tests were less frequent (e.g. once per year, instead of once every 6 months) would you be willing to have this test? Yes <input type="checkbox"/> No <input type="checkbox"/>

2. WOULD YOU CONSENT TO A BREATH TEST WHEN YOU COME TO CLINIC ?	
Yes <input type="checkbox"/>	No <input type="checkbox"/> Please give reasons you would not want to have this: If the tests were less frequent (e.g. once per year, instead of once every 6 months) would you be willing to have this test? Yes <input type="checkbox"/> No <input type="checkbox"/>

3. WOULD YOU CONSENT TO ANOTHER CT SCAN SHORTLY BEFORE YOU COME TO CLINIC ?

Yes No

Please give reasons you would not want to have this:

If the tests were less frequent (e.g. once per year, instead of once every 6 months) would you be willing to have this test?

Yes No

4. WOULD YOU CONSENT TO AN MRI SCAN SHORTLY BEFORE YOU COME TO CLINIC ?

Yes No

Please give reasons you would not want to have this:

If the tests were less frequent (e.g. once per year, instead of once every 6 months) would you be willing to have this test?

Yes No

The next two questions relate to your views on having repeat fluid or biopsy samples taken during the next 2 years.

These procedures would be performed by the same doctors who did your recent tests. The test would be performed based on careful assessments made during your clinic visits and only if it was thought to be safe and appropriate.

5. WOULD YOU CONSENT TO REPEAT PLEURAL FLUID SAMPLING?

Yes No

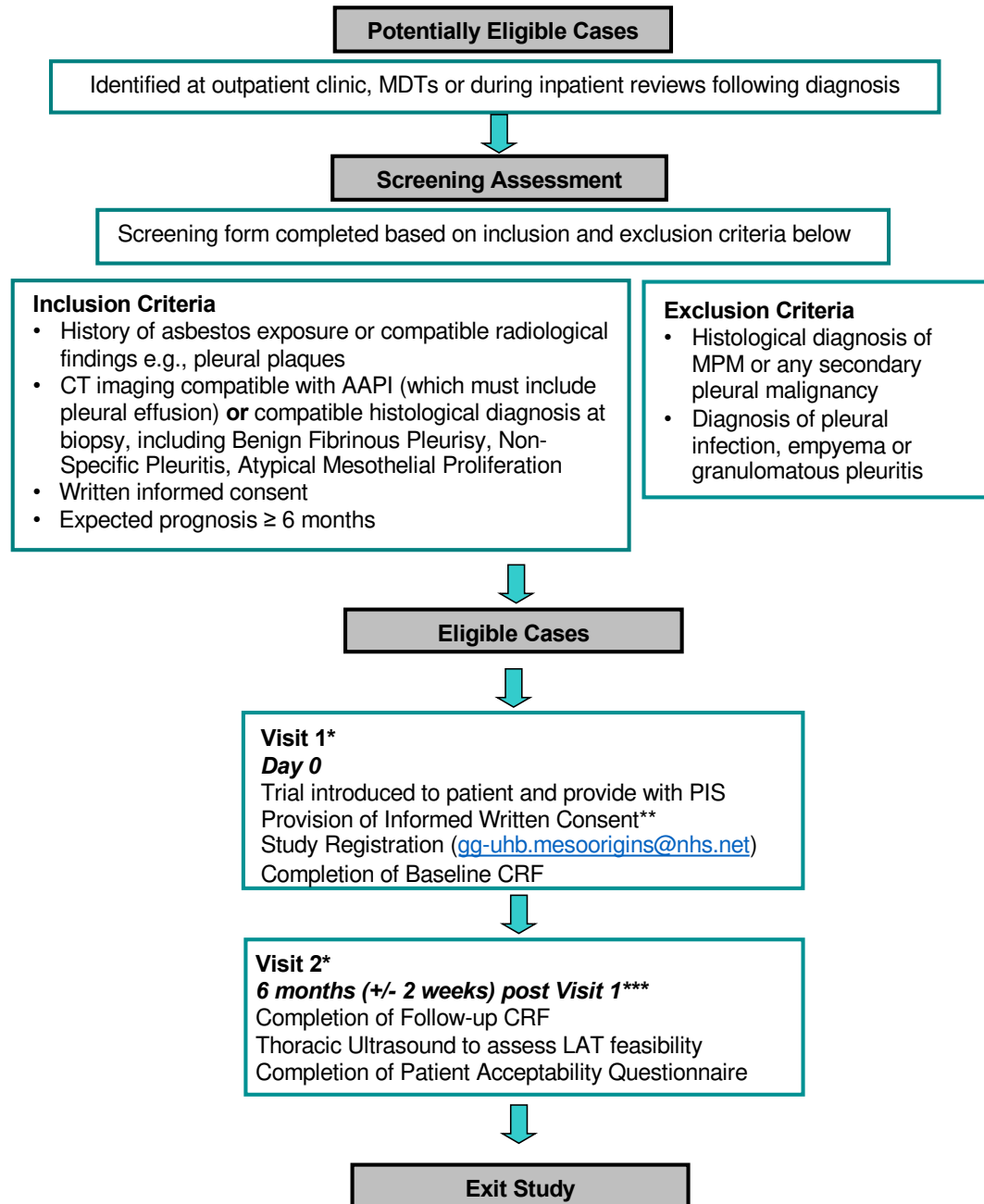
Please give reasons you would not want to have this:

6. WOULD YOU CONSENT TO REPEAT THORACOSCOPY AND BIOPSY?

Yes No

Please give reasons you would not want to have this:

SECTION 3: PROSPECTIVE STUDY FLOWCHART



*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 ≥ 6 months after initial BAPE diagnosis, then visit 1 and 2 can be combined at day 0.

SECTION 4: BASELINE CHARACTERISTICS IN PROSPECTIVE STUDY RECRUITS WITH HISTOLOGICAL v RADIOLOGICAL DIAGNOSES.

Characteristic	Histological Diagnosis (n=21)	Radiological Diagnosis (n=18)	p-value
Age	74 (53-84)	76.5 (63-88)	0.2534
Male Gender	21 (100%)	18 (100%)	>0.9999
Asbestos Exposed	21 (100%)	18 (100%)	>0.9999
Pleural Effusion Characteristics:			
• Right-sided	12 (57%)	7 (39%)	0.3406
• Unilateral	21 (100%)	17 (94%)	0.4615
• <50% of hemithorax on erect chest radiograph	16 (76%)	17 (94%)	0.1897
Findings on CT imaging			
• Pleural Plaques	15 (71%)	16 (89%)	0.2472
• Malignant Features	4 (19%)	1 (6%)	0.3489

CT: Computed Tomography. Values are reported as median (range) or n (%).

SECTION 5: TUS FINDINGS REGARDING REPEAT LAT FEASIBILITY

Local Anaesthetic Thoracoscopy (LAT) feasibility was assessed indirectly by thoracic ultrasound (TUS) at the single follow-up visit in the prospective study. 28/39 cases recruited completed this visit and had data available for analysis.

A pleural effusion was present in 20/28 (71%) patients and LAT was deemed technically feasible in 13/28 (46%). TUS features associated with LAT feasibility are summarised in the table below. TUS-guided needle biopsy (TUS-GNB) was recorded as a technically feasible alternative in 3/28 (11%) recruits. Re-biopsy by LAT or TUS-GNB was therefore feasible in 16/28 (57%) assessable patients.

TUS feature	LAT Feasible n=13	LAT Not Feasible n=15	p-value
Pleural effusion present	11/13 (85%)	9/15 (60%)	0.2213
Character of effusion when present			
• Size (Median # of rib spaces occupied by fluid)	3 (1-4)	1 (1-3)	0.0097
• Any septations reported	1/11 (9%)	2/9 (22%)	0.5658
• Septations judged severe enough to preclude LAT	0/11 (0%)	2/9 (22%)	>0.9999
• Associated lung sliding	8/11 (73%)	2/9 (22%)	0.0698
Lung sliding present	10/13 (77%)	6/15 (40%)	0.0671
Character of Lung Sliding when present			
• Sliding associated with effusion	8/13 (62%)	2/15 (13%)	0.0163
• Sliding associated with no effusion	2/13 (15%)	4/15 (27%)	0.6546
• Extent of sliding (median # of positions with sliding)	4 (1-6)	4.5 (2-8)	0.4080

Values reported as simple proportions, median (range) or n (%)

Conclusion

LAT feasibility was frequently associated with the presence of a reasonably large pleural effusion, which was rarely septated, and the presence of lung sliding. Pleural effusion was commonly observed in cases in which LAT was deemed non-feasible, but the effusion tended to be smaller and more frequently septated. Lung sliding was observed in a significant proportion of apparently non-feasible cases (40%), including those without pleural effusion (27%). In the future Meso-ORIGINS study, these dry but not pleurodesed spaces might be accessible by pneumothorax induction in centres with appropriate training and support. Image-guided biopsy, including by TUS-GNB will be an alternative method in some patients in whom LAT is not feasible.