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 ASSESSMENT 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: DD / MON / YYYY

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 ☐ 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 ☐

2. WOULD YOU CONSENT TO A BREATH TEST WHEN 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 ☐
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

**Potentially Eligible Cases**
Identified at outpatient clinic, MDTs or during inpatient reviews following diagnosis

**Screening Assessment**
Screening form completed based on inclusion and exclusion criteria below

### Inclusion Criteria
- History of asbestos exposure or compatible radiological findings e.g., pleural plaques
- CT imaging compatible with AAPI (which must include pleural effusion) or compatible histological diagnosis at biopsy, including Benign Fibrinous Pleurisy, Non-Specific Pleuritis, Atypical Mesothelial Proliferation
- Written informed consent
- Expected prognosis $\geq$ 6 months

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

**Eligible Cases**

**Visit 1**
*Day 0*
Trial introduced to patient and provide with PIS
Provision of Informed Written Consent**
Study Registration (gg-uhb.mesoorigins@nhs.net)
Completion of Baseline CRF

**Visit 2**
6 months (+/- 2 weeks) post Visit 1***
Completion of Follow-up CRF
Thoracic Ultrasound to assess LAT feasibility
Completion of Patient Acceptability Questionnaire

**Exit Study**

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*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 26months 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.

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

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.

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

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.