# Meso-ORIGINS

**Part of the PREDICT-Meso International Accelerator Network**

| | |
|---|---|
| **ISRCTN No:** | ISRCTN22929761 |
| **Protocol No:** | 2.0 15Jan24 |
| **IRAS No:** | 291818 |
| **REC No:** | 21/WS/0120 |
| **Sponsor Ref:** | GN19ON232 |
| **Sponsor:** | NHS Greater Glasgow & Clyde |
| **Funder:** | Cancer Research UK |
| **Grant Reference:** | C57060/A29372 |

Funded by

**AUTHORISED BY:**

**Name:** Kevin Blyth **Role:** Chief Investigator

**Date:** 15th January 2024 **SIGNATURE:**

## STUDY MANAGEMENT GROUP

### CHIEF INVESTIGATOR

**Professor Kevin Blyth**
Professor of Respiratory Medicine
University of Glasgow
Queen Elizabeth University Hospital
1345 Govan Road
Glasgow G51 4TF
☎ 0141 451 6163
kevin.blyth@glasgow.ac.uk

### CLINICAL STUDY COORDINATOR

**Dr Mark Neilly**
Clinical Research Fellow
Department of Respiratory Medicine
Queen Elizabeth University Hospital
1345 Govan Road
Glasgow G51 4TF
☎ 0141 451 6099
Mark.Neilly@ggc.scot.nhs.uk

### CO-INVESTIGATORS

**Dr Selina Tsim**
MacMillan Consultant in Respiratory Medicine
Queen Elizabeth University Hospital
1345 Govan Road
Glasgow G51 4TF
☎ 07492999818
selina.tsim@ggc.scot.nhs.uk

**Professor Nick Maskell**
Professor of Respiratory Medicine
University of Bristol Academic Respiratory Unit
Southmead Hospital
Bristol BS10 5NB
☎ 0117 414 8048
nick.maskell@bristol.ac.uk

**Professor Najib Rahman**
Professor of Respiratory Medicine
Oxford Respiratory Trials Unit
Oxford Radcliffe Hospital
Churchill Hospital Site
Oxford OX3 7LE
☎ 01865 225205
najib.rahman@ndm.ox.ac.uk

**Dr Robert Rintoul**
Reader in Thoracic Oncology
University of Cambridge
Department of Thoracic Oncology
Royal Papworth Hospital
Cambridge CB2 0AY
☎ Academic PA 01223 768433
robert.rintoul@nhs.net

**Dr Kevin Lamote**
Postdoctoral Researcher
Translational Research in Immunology &Inflammation
University of Antwerp
Universiteitsplein 1,2610 Wilrijk
Belgium
☎ +32 (0)65 25 81
Kevin.Lamote@uantwerpen.be

**Professor Jan Van Meerbeeck**
Thoracic Oncology
Antwerp University Hospital
University Hospital of Antwerp - UZA
Wilrijkstraat 10, 2650 Antwerpen-Edegem
Belgium
☎ +32 (0)3 821 50 89
Jan.VanMeerbeeck@uza.be

### PREDICT-Meso PROJECT MANAGER

**Dr Alexandrea MacPherson**
Institute of Cancer Sciences
University of Glasgow
Garscube Estate, Switchback Road, Bearsden
Glasgow G61 1QH
alexandrea.macpherson@glasgow.ac.uk

### BIOINFORMATICS LEAD

**Professor Crispin Miller**
Head of Bioinformatics
Beatson Institute for Cancer Research
Switchback Road, Bearsden
Glasgow G61 1BD
crispin.miller@glasgow.ac.uk

**CTU PROJECT MANAGER**
**Laura Alexander**
Cancer Research UK Clinical Trials Unit
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow G12 0YN
☎ 0141 301 7212
✉ laura.alexander@glasgow.ac.uk

**STUDY STATISTICIAN**
**Joshua Roche**
Institute of Cancer Sciences
University of Glasgow
Garscube Estate, Switchback Road, Bearsden
Glasgow G61 1QH
✉ 2835723r@student.gla.ac.uk

**PHARMACOVIGILANCE MANAGER**
**Jacqui Gourlay**
Cancer Research UK Clinical Trials Unit
Level 0 Room G/24, Admin Building
1055 Great Western Road
Glasgow G12 0XH
☎ 0141 211 0352
✉ mvls-ctu-pv@glasgow.ac.uk

**PHARMACOVIGILANCE CTC**
**Jennifer Flach**
Cancer Research UK Clinical Trials Unit
Level 0 Room G/24, Admin Building
1055 Great Western Road
Glasgow G12 0XH
☎ 0141 232 2068
✉ mvls-ctu-pv@glasgow.ac.uk

**SPONSOR REPRESENTATIVE**
**Joanne McGarry**
Sponsor Research Coordinator
NHS Greater Glasgow and Clyde
Research & Innovation
Ward 11
Dykebar Hospital
Grahamston Road
☎ 0141 314 4001
✉ joanne.mcgarry@ggc.scot.nhs.uk

**CLINICAL TRIAL CO-ORDINATOR**
**Nicola Walker**
Cancer Research UK Clinical Trials Unit
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow G12 0YN
☎ 0141 301 7195
✉Nicola.Walker.2@glasgow.ac.uk

**PPI REPRESENTATIVE**
**Julie Roberts**
✉ juliecroberts@hotmail.com

**RADIOLOGY LEAD**
**Dr Gordon Cowell**
Consultant Radiologist
Department of Imaging
Queen Elizabeth University Hospital
1345 Govan Road
Glasgow G51 4TF
✉ gordon.cowell@ggc.scot.nhs.uk

This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition; 2006) and World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended)

**Protocol Authorised by:**

Name: Kevin Blyth
Role: Chief Investigator
Date: 15th January 2024

Signature: 

Name: Joshua Roche
Role: Study Statistician
Date: 15th January 2024
Signature: 

Name: Joanne McGarry
Role: Sponsor Representative
Date: 15th January 2024

Signature: 

<table>
<tr><th colspan="3">SUMMARY</th></tr>
<tr><td>Title</td><td colspan="2">Meso-ORIGINS: Mesothelioma Observational study of RIsk prediction and Generation of paired benign-meso tissue samples, Including a Nested MRI Sub-study</td></tr>
<tr><td>Background & Rationale</td><td colspan="2">Malignant Pleural Mesothelioma (MPM) is universally fatal but heterogeneous in terms of prognosis and response to current therapies. MPM typically develops decades after asbestos exposure and is often presaged by radiological and clinical evidence of chronic pleural inflammation. A better understanding of the driving and/or permissive events involved in MPM evolution would enhance MPM drug design and facilitate future human trials of novel agents. Meso-Origins will generate a large cohort of paired tissue samples from patients with asbestos-associated benign pleural inflammation. This will include patients who progress to MPM (Benign-MPM Evolution pairs) and those who do not (Benign-No MPM evolution pairs) over 2 years of clinical follow-up. The tissue collected will be subject to multiomic molecular characterisation in downstream PREDICT-Meso work-packages and will be used to generate a suite of new pre-clinical MPM models, for high-throughput drug screening and in target-drug validation. Tumour heterogeneity will be studied by collection of multi-region pleural biopsies in patients presenting with MPM.</td></tr>
<tr><td>Study Design</td><td colspan="2">Multi-centre, prospective observational study, incorporating two arms (Arm A and Arm B) and a cross-sectional MRI sub-study within Arm A</td></tr>
<tr><td>Study Population</td><td colspan="2">Arm A:<ul><li>500 patients with asbestos-associated benign pleural disease, including at least 63 patients who will develop MPM during subsequent 2-year follow up.</li><li>100/500 patients will be recruited to the MRI sub-study</li></ul>Arm B:<ul><li>250 asbestos exposed patients with suspected MPM, generating multi-region pleural biopsies in at least 91 MPM patients for heterogeneity analyses</li></ul></td></tr>
<tr><td rowspan="3">Primary</td><td>Objectives</td><td>Endpoints</td></tr>
<tr><td>To create a prospective cohort of patients with asbestos-associated benign pleural disease, of whom an estimated 63 patients will develop MPM within 2 years</td><td>Number of patients in Arm A diagnosed with MPM at any point from study registration to completion of 2 years follow-up</td></tr>
<tr><td></td></tr>
<tr><td rowspan="2">Secondary</td><td>To generate a risk prediction model for evolution of MPM within 2 years, based on serum proteomics, exhaled breath metabolomics and perfusion MRI</td><td>Results of a multiomic risk classifier based on radiomic, proteomic and metabolic measurements in patients at baseline in Arm A</td></tr>
<tr><td>To collect spatially distinct tumour biopsies from patients with MPM, facilitating comprehensive characterisation of intra-patient tumour heterogeneity</td><td>Number of patients in the Arm B with histologically confirmed MPM following thoracoscopy</td></tr>
<tr><td rowspan="2">Eligibility Criteria</td><td colspan="2">ARM A</td></tr>
<tr><td>Inclusion Criteria<ul><li>History of asbestos exposure or imaging compatible with this (e.g., pleural plaques)</li></ul></td><td>Exclusion Criteria<ul><li>Any cytologically or histologically confirmed pleural malignancy</li><li>Any pleural infection including TB</li></ul></td></tr>
</table>

| SUMMARY | | |
|---|---|---|
| | • Any form of pleural tissue biopsy within last 1 year showing evidence of associated pleural inflammation (e.g., benign fibrinous pleurisy, non-specific pleuritis, atypical mesothelial proliferation, mesothelioma in situ)<br>• ≥16 years of age<br>• Informed written consent to at least banking of any previous and future pleural tissue samples | • Granulomatous pleural inflammation<br>• Any specific pleuritis (e.g., RA)<br>• Previous Pleurodesis<br><br>**NB:** Clinical suspicion of MPM after initial negative (benign) biopsy is **NOT** an exclusion criterion. This includes patients with malignant-looking CT imaging who are **NOT** excluded. |
| | **ARM A: MRI SUB-STUDY** | |
| | **Inclusion Criteria:**<br>• Registered to the Arm A<br>• Informed written consent | **Exclusion Criteria:**<br>• Any contraindication to MRI, e.g., claustrophobia, pregnancy, metallic foreign body, pacemaker/implant, unable to lie flat<br>• Allergy to gadolinium contrast<br>• eGFR <30 ml/min |
| | **ARM B** | |
| | **Inclusion Criteria**<br>• Suspected pleural malignancy, defined by a unilateral pleural effusion or mass<br>• History of asbestos exposure or typical radiological features e.g., pleural plaques<br>• Sufficient fitness for thoracoscopy (LAT or VATS are permissible)<br>• ≥16 years of age<br>• Informed written consent | **Exclusion Criteria**<br>• Current or recent (within last 3 months) intercostal chest drain<br>• Previous Pleurodesis |
| **Study Procedures** | **ARM A** | |
| | Following consent and registration, baseline data, blood and exhaled breath samples will be collected. Participants will have 6-monthly study visits for 2-years, Suspicion of MPM evolution will prompt repeat biopsy and fluid sampling. Participants with reassuring follow-up (≥18 months) will also be approached for repeat sampling, based on technical feasibility, as assessed by thoracic ultrasound and acceptability. | |
| | **ARM A: MRI SUB-STUDY** | |
| | At participating centres only, patients separately consented and registered. Contrast-enhanced MRI will be performed within 14 (+/-10) days of registration to Arm A. | |
| | **ARM B** | |
| | Participants will be identified via urgent suspected cancer pathways. Following consent and registration, blood and multi-region research biopsies will be banked during diagnostic thoracoscopy (LAT or VATS are permissible). | |
| **Study Period** | Recruitment Period: 41 months. Per Patient duration: Arm A; 24 months, Arm B; 28 days | |

TABLE OF CONTENTS


**1 ABBREVIATIONS ..... 11**

**2 STUDY FLOWCHARTS ..... 13**

2.1 ARM A ..... 13

2.2 ARM B ..... 14

**3 SCHEDULE OF ASSESSMENTS ..... 15**

3.1 ARM A ..... 15

3.2 ARM B ..... 17

**4 INTRODUCTION ..... 18**

4.1 BACKGROUND AND AIMS ..... 18

4.2 BENIGN PLEURAL INFLAMMATION AND MPM ..... 18

4.3 MESO-ORIGINS FEASIBILITY STUDY ..... 18

4.4 TISSUE SAMPLING IN MESOTHELIOMA ..... 19

4.5 HETEROGENEITY ..... 19

4.6 NON-INVASIVE TOOLS FOR DETECTION OF MPM ..... 20

4.7 STUDY RATIONALE ..... 20

**5 STUDY OBJECTIVES ..... 21**

5.1 PRIMARY OBJECTIVE ..... 21

5.2 SECONDARY OBJECTIVES ..... 21

**6 STUDY DESIGN ..... 21**

6.1 STUDY POPULATION ..... 21

*6.1.1 Arm A ..... 21*

6.1.1.1 MRI Sub-study ..... 21

*6.1.2 Arm B ..... 21*

6.2 ELIGIBILITY CRITERIA ..... 22

*6.2.1 Arm A ..... 22*

6.2.1.1 Arm A – MRI sub-study ..... 22

*6.2.2 Arm B ..... 22*

6.3 IDENTIFICATION OF PARTICIPANTS AND CONSENT ..... 23

*6.3.1 Arm A ..... 23*

6.3.1.1 Arm A: MRI sub-study ..... 23

*6.3.2 Arm B ..... 23*

6.4 Registration ..... 23
6.5 Remote Observation ..... 24
6.6 Withdrawal of Participants from the study ..... 24
6.7 Co-enrolment Guidelines ..... 24

**7 STUDY ENDPOINTS ..... 24**

7.1 Primary Endpoint ..... 24
7.2 Secondary Endpoints ..... 24

**8 STUDY ACITIVITIES: ARM A ..... 25**

8.1 Visit A1: baseline (Day 1) ..... 25
8.2 Visit A2: MRI (Day 15 ± 10 days) ..... 26
8.3 Visit A3: Follow-up #1 (6 months ± 4 weeks) ..... 26
8.4 Visit A4: Follow-up #2 (12 months ± 4 weeks) ..... 26
8.5 Visit A5: Follow-up #3 (18 months ± 4 weeks): ..... 27
8.6 Visit A6: Follow-up #4 (24 months ± 4 weeks) ..... 27
8.7 Visit A7: Repeat biopsy screening (UP TO 4 weeks following visit A5 *or* A6) ..... 28
8.8 Visit A8: Repeat biopsy (UP TO 2 weeks following TUS SCREENING) ..... 28
8.9 Visit A9: Post-repeat biopsy (up to 2 weeks post-visit A8) ..... 28

**9 STUDY ACTIVITIES: ARM A REMOTE OBSERVATION ..... 29**

**10 STUDY ACTIVITES: ARM B ..... 29**

10.1 Visit B1: Baseline (DAY 1) ..... 29
10.2 Visit B2: Thoracoscopy (DAY 15 ± 14 DAYS) ..... 29
10.3 Visit B3: Post-thoracoscopy (DAY 29 ± 14 DAYS) ..... 30

**11 LABORATORY TESTS ..... 30**

**12 PLEURAL BIOPSY RETRIEVAL AND RETURN ..... 30**

12.1 Sample return process ..... 31

**13 ASSESSMENT OF SAFETY ..... 31**

13.1 LAT and VATS ..... 31
13.2 Contrast-enhanced MRI (for MRI sub-study) ..... 31

**14 SAFETY REPORTING ..... 32**

14.1 Definitions ..... 32
14.2 Detecting, Recording and Reporting of Adverse Events ..... 33

*14.2.1 Detection of Adverse Events* ..... *33*
*14.2.2 Recording of Adverse Events* ..... *33*
*14.2.3 Assessment of Adverse Events* ..... *33*
*14.2.4 Reporting of a Serious Adverse Event* ..... *34*
14.3 EXPECTED EVENTS ..... 34
*14.3.1 Venous Blood Sampling* ..... *34*
*14.3.2 Exhaled Breath Tests* ..... *34*
*14.3.3 Chest Radiograph* ..... *35*
*14.3.4 Magnetic Resonance Imaging (MRI)* ..... *35*
*14.3.5 Local Anaesthetic Thoracoscopy (LAT)* ..... *35*
*14.3.6 Video-assisted Thoracoscopic Surgery (VATS)* ..... *35*
*14.3.7 Image-guided Pleural Biopsy* ..... *36*
14.4 IDENTIFYING EVENTS FOR EXPEDITED REPORTING ..... 36
14.5 EXPEDITED REPORTS ..... 36
14.6 PREGNANCY REPORTING ..... 37
14.7 STUDY INTERVENTION ERRORS ..... 37
14.8 ANNUAL PROGRESS REPORT ..... 37
14.9 MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA) REPORTING ..... 37
**15 STATISTICS AND DATA ANALYSIS ..... 37**
15.1 SAMPLE SIZE AND ASSUMPTIONS ..... 37
15.2 ANALYSIS PLAN ..... 38
*15.2.1 Primary Endpoint Analysis* ..... *38*
*15.2.2 Secondary Endpoint Analyses* ..... *38*
*15.2.3 Safety Analysis* ..... *39*
*15.2.4 Interim Analyses* ..... *39*
**16 STUDY CLOSURE/DEFINITION OF END OF THE STUDY ..... 39**
16.1 END OF STUDY NOTIFICATION/DECLARATION OF THE END OF A STUDY FORM ..... 39
16.2 CLINICAL STUDY SUMMARY REPORT ..... 39
16.3 TEMPORARY HALT OF THE STUDY ..... 39
16.4 EARLY TERMINATION OF A STUDY ..... 39
**17 DATA HANDLING ..... 39**
17.1 ELECTRONIC CASE REPORT FORMS (ECRFS) ..... 39
17.2 CENTRAL REVIEW OF DATA ..... 40

17.3 Data Escalation Processes ..... 40
17.4 Record Retention and archiving ..... 40

**18 STUDY MANAGEMENT ..... 41**

18.1 STUDY Start Up ..... 41
18.2 Core Documents ..... 41
18.3 Management of Protocol Deviations and Violations ..... 41
*18.3.1 Deviations ..... 41*
*18.3.2 Serious Breach ..... 41*
18.4 Study Management Group (SMG) ..... 41

**19 REGULATORY ISSUES ..... 42**

19.1 Ethics Approval ..... 42
19.2 Consent ..... 42
19.3 Confidentiality ..... 43
19.4 Liability, Indemnity and Insurance ..... 43
19.5 Sponsor ..... 43
19.6 Funding ..... 43
19.7 Protocol Amendments ..... 44
19.8 Allocation of Study Responsibilities ..... 44
*19.8.1 Sponsor Responsibilities (NHS GG&C) ..... 44*
*19.8.2 Chief Investigator (CI) ..... 44*
*19.8.3 PREDICT-Meso Network ..... 44*
*19.8.4 CRUK Clinical Trials Unit (CTU) ..... 44*
*19.8.5 Participating Site ..... 44*
*19.8.6 Principal Investigator (PI) ..... 44*

**20 QUALITY ASSURANCE ..... 45**

20.1 Audits and Inspections ..... 45
20.2 On Site and Telephone Monitoring ..... 45
20.3 Protocol Non-compliance ..... 45

**21 PUBLICATION POLICY ..... 45**

**22 DATA OWNERSHIP ..... 45**

**23 REFERENCES ..... 47**

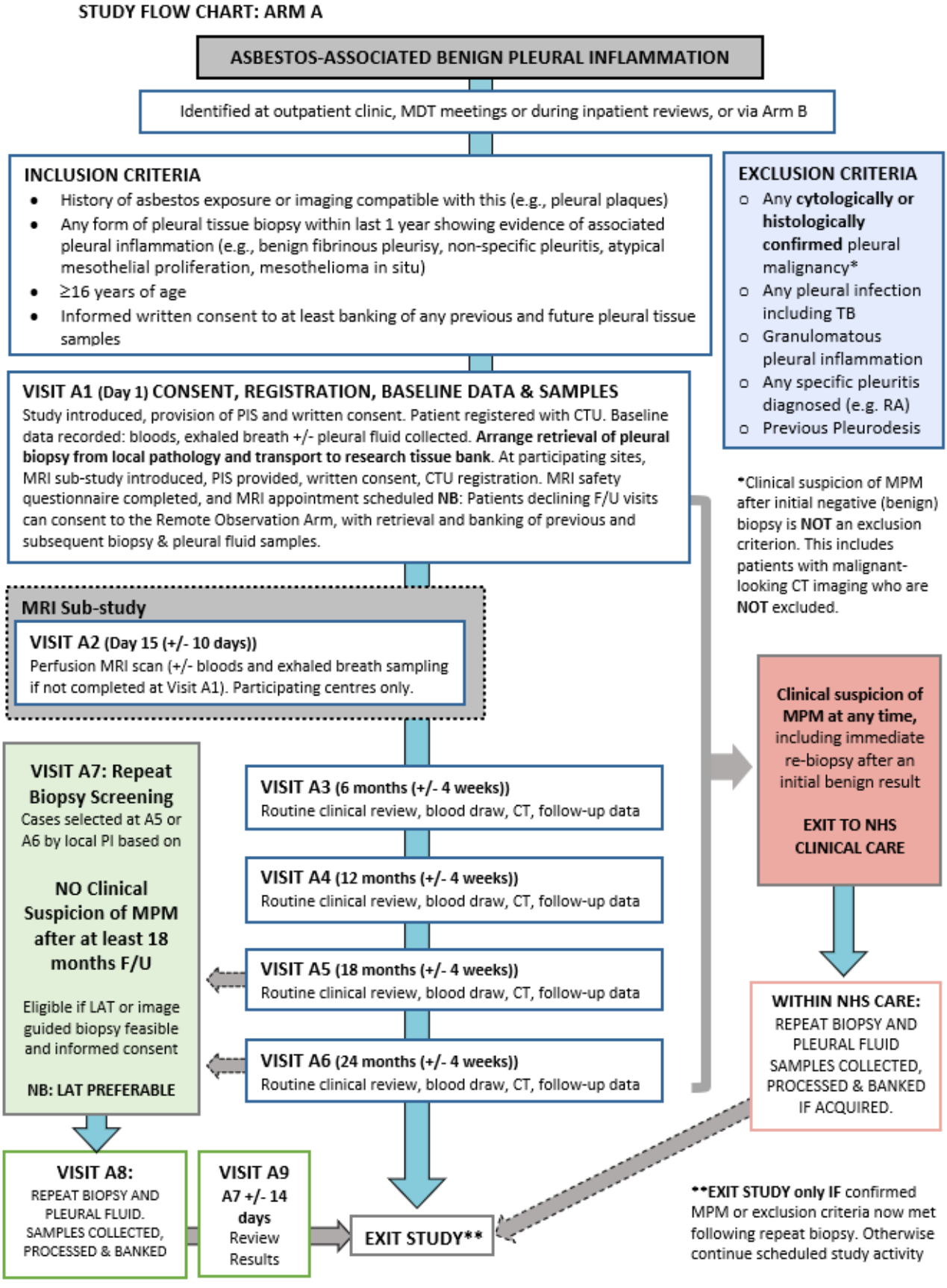
# 1 ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| AE | Adverse Event |
| ALS | Adult Life Support |
| BP | Blood Pressure |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CRP | C-Reactive Protein |
| CRUK | Cancer Research United Kingdom |
| CT | Computed Tomography |
| CTC | Clinical Trials Coordinator |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIMP | Clinical Trial of an Investigational Medicinal Product |
| CTU | Clinical Trials Unit |
| ECG | Electrocardiograph |
| eCRF | Electronic Case Report Form |
| eGFR | estimated Glomerular Filtration Rate |
| eRDC | electronic Remote Data Capture |
| FBC | Full Blood Count |
| FFPE | Formalin-Fixed Paraffin Embedded |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HRA | Health Research Authority |
| ISF | Investigator site file |
| ITH | Intra-Tumour Heterogeneity |
| LAT | Local Anaesthetic Thoracoscopy |
| LDH | Lactate Dehydrogenase |
| MDT | Multi-Disciplinary Team Meeting |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MoU | Memorandum of Understanding |
| MPM | Malignant Pleural Mesothelioma |
| MRI | Magnetic Resonance Imaging |
| NCI | National Cancer Institute |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NHS GG&C | NHS Greater Glasgow & Clyde |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| PM | Project Manager |
| RA | Rheumatoid Arthritis |
| R&D | Research and Development |
| RAE | Related Adverse Event |
| REC | Research Ethics Committee |
| RSI | Reference Safety Information |

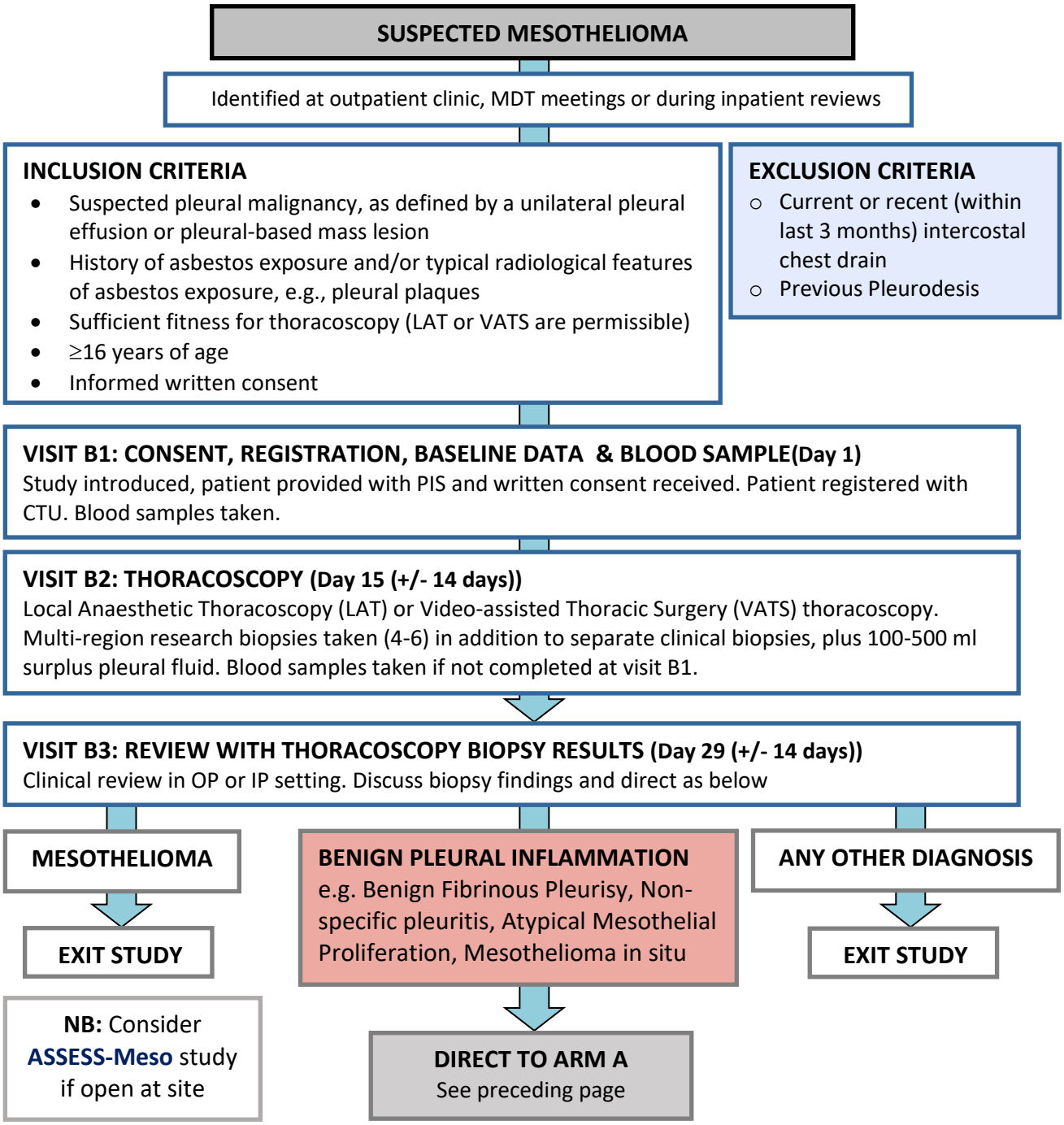
| Abbreviation | Term |
|---|---|
| SAE | Serious Adverse Event |
| SMG | Study Management Group |
| SOP | Standard Operating Procedure |
| SRAE | Serious and Related Adverse Event |
| SSC | Study Steering Committee |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| TUS | Thoracic Ultrasound |
| US | Ultrasound |
| USOC | Urgent Suspicion of Cancer |
| U&E | Urea & Electrolytes |
| VATS | Video-Assisted Thoracoscopic Surgery |

# 2 STUDY FLOWCHARTS

## 2.1 ARM A



## 2.2 ARM B


SUSPECTED MESOTHELIOMA
Identified at outpatient clinic, MDT meetings or during inpatient reviews
INCLUSION CRITERIA
Suspected pleural malignancy, as defined by a unilateral pleural effusion or pleural-based mass lesion
History of asbestos exposure and/or typical radiological features of asbestos exposure, e.g., pleural plaques
Sufficient fitness for thoracoscopy (LAT or VATS are permissible)
≥16 years of age
Informed written consent
EXCLUSION CRITERIA
Current or recent (within last 3 months) intercostal chest drain
Previous Pleurodesis
VISIT B1: CONSENT, REGISTRATION, BASELINE DATA & BLOOD SAMPLE(Day 1)
Study introduced, patient provided with PIS and written consent received. Patient registered with CTU. Blood samples taken.
VISIT B2: THORACOSCOPY (Day 15 (+/- 14 days))
Local Anaesthetic Thoracoscopy (LAT) or Video-assisted Thoracic Surgery (VATS) thoracoscopy. Multi-region research biopsies taken (4-6) in addition to separate clinical biopsies, plus 100-500 ml surplus pleural fluid. Blood samples taken if not completed at visit B1.
VISIT B3: REVIEW WITH THORACOSCOPY BIOPSY RESULTS (Day 29 (+/- 14 days))
Clinical review in OP or IP setting. Discuss biopsy findings and direct as below
MESOTHELIOMA
EXIT STUDY
NB: Consider ASSESS-Meso study if open at site
BENIGN PLEURAL INFLAMMATION
e.g. Benign Fibrinous Pleurisy, Non-specific pleuritis, Atypical Mesothelial Proliferation, Mesothelioma in situ
DIRECT TO ARM A
See preceding page
ANY OTHER DIAGNOSIS
EXIT STUDY

# 3 SCHEDULE OF ASSESSMENTS

## 3.1 ARM A

| Visit Number | A1 | A2 | A3 | A4 | A5 | A6 | A7 | A8 | A9 |
|---|---|---|---|---|---|---|---|---|---|
| Approximate Study Day | 1[1] | 15d (± 10d) | 6m (±4w) | 12m (±4w) | 18m (±4w) | 24m (±4w) | ≤4W post A5/6 | ≤2W post A7 | ≤2W post A8 |
| **Routine Clinical Activity** | | | | | | | | | |
| Clinical review | X | | X | X | X | X | | | |
| Contrast-enhanced CT Thorax[2] | X | | X | X | X | X | | | |
| Arrange repeat imaging +/- biopsy if clinically indicated (suspected progression to MPM)[3] | X | | X | X | X | X | | | |
| **Study Activity** | | | | | | | | | |
| Review Eligibility Criteria | X | | | | | | | | |
| If potentially eligible, introduce study[4], provide with PIS and discuss participation[5] | X | | | | | | | | |
| Informed Written Consent | X | X[6] | | | | | | | |
| Register participant with CTU | X | X[6] | | | | | | | |
| Record Baseline Data[7] | X | X[6] | | | | | | | |
| Blood Sampling, Processing and Banking[8] | X | X[6] | X | X | X | X | | | |
| Exhaled Breath Sampling and Processing[9] | X | X[6] | | | | | | | |
| Bank Pleural Fluid sample if IPC in-situ[10] | X | X[6] | | | | | | | |
| Arrange retrieval of FFPE pleural tissue biopsies from local pathology and transport to RTB | X | X[6, 11] | | | | | | | X[11] |
| Bank any repeat pleural biopsies +/- fluid if **CLINICAL SUSPICION OF MESOTHELIOMA** | At any time from registration to study exit[10, 11] | | | | | | | | |
| Discuss possibility of repeat biopsy if **NO CLINICAL SUSPICION OF MESOTHELIOMA** | | | | | X | X | | | |
| If acceptable and potentially feasible, screen by TUS *or* arrange formal screening visit (A7) | | | | | X | X | | | |
| TUS screening for feasibility of repeat biopsy (ideally LAT but can be image guided biopsy) | | | | | X | X | X[6] | | |
| Repeat Pleural Biopsy (+ fluid if available)[3] | | | | | | | | X[8] | |
| Chest Radiograph post-biopsy (within 1-12h) | | | | | | | | X | |
| Clinical Review with Repeat Sampling Results | | | | | | | | | X |
| Record Follow-up Data | | | X | X | X | X | X | X | X |
| Record Adverse Events | X | X | X | X | X | X | X | X | X |

| Visit Number | A1 | A2 | A3 | A4 | A5 | A6 | A7 | A8 | A9 |
|---|---|---|---|---|---|---|---|---|---|
| **MRI Sub-study Activity** [12] | | | | | | | | | |
| Review Eligibility Criteria | X | | | | | | | | |
| Introduce MRI sub-study if eligible | X | | | | | | | | |
| Provide separate MRI sub-study PIS | X | | | | | | | | |
| Discussion and Written Informed Consent | X | X [6] | | | | | | | |
| Register participant to sub-study with CTU | X | X [6] | | | | | | | |
| Arrange a date for MRI | X | | | | | | | | |
| MRI Safety Questionnaire | X | X [6] | | | | | | | |
| Orbital Radiograph, if indicated [13] | | X | | | | | | | |
| Contrast-enhanced MRI Thorax [14] | | X | | | | | | | |

1. Visit A1 activities should ideally be completed on the same day but can be completed over up to 7d (see d)
2. A baseline contrast-enhanced CT Thorax should ideally be available within 12 weeks of visit A1 to confirm participant has not progressed since original benign biopsy. If not available, repeat CT should be considered based on clinical judgement but is not mandatory
3. Please refer to Meso-ORIGINS Biopsy Manual
4. Investigators may introduce the study at earlier clinic visits if eligibility likely and clinically appropriate
5. PIS can be provided either in person or remotely. Participants will be offered a follow-up telephone call with a member of the study team if they wish more time to consider the study. This call will occur no later than 2 working days after provision of PIS.
6. If not already performed
7. Including the following baseline blood results from patient records, which should be repeated if not available within 4 weeks of visit A1: full blood count, lactate dehydrogenase, c-reactive protein, albumin, urea and electrolytes. Baseline data also includes results of previous pleural fluid, pleural biopsy and imaging tests performed as part of routine clinical care.
8. Please refer to Meso-ORIGINS Sample Handling Manual
9. Please refer to Meso-ORIGINS Exhaled Breath Sampling Manual. Exhaled breath samples can be omitted at sites where facilities are not in place for acquisition or storage, or on grounds of patient preference
10. It is acknowledged that not all patients will have pleural fluid available for banking, via an indwelling pleural catheter (IPC). Where available a sample should be drawn and banked. Please refer to the Meso-ORIGINS Sample Handling Manual for detailed instructions
11. FFPE biopsy blocks from diagnosis of BENIGN PLEURAL INFLAMMATION and histological confirmation of MESOTHELIOMA EVOLUTION and NO MESOTHELIOMA EVOLUTION should all be retrieved from the local pathology archive and transported to the PREDICT-Meso Research Tissue Bank (RTB), based in Glasgow. Please refer to the Meso-ORIGINS Sample Handling Manual for detailed instructions
12. Only offered to participants in participating centres
13. Orbital Radiograph only if required to exclude a foreign body, based on relevant history
14. Please refer to Meso-ORIGINS MRI Manual

### 3.2 ARM B

| Visit Number | B1 | B2 | B3 |
|---|---|---|---|
| Approximate Study Day | 1 | 15d (±14d) | 29d (±14d) |
| **Routine Clinical Activity** | | | |
| Clinical review to assess for suspected MPM | X | | |
| TUS assessment for LAT feasibility [a] | X | | |
| Contrast-enhanced CT Thorax [b] | X | | |
| Thoracoscopy (LAT or VATS) with pleural biopsies and fluid sent for diagnostic purposes [c] | | X | |
| Chest Radiograph post-procedure (within 1-12h) | | X | |
| Clinical review with results of pleural sampling | | | X |
| **Study Activity** | | | |
| Review Eligibility Criteria | X | | |
| If potentially eligible, introduce study [d], provide with PIS and discuss participation [e] | X | | |
| Informed Written Consent | X | X [f] | |
| Register participant with CTU | X | X [f] | |
| Record Baseline Data [g] | X | X [f] | |
| Blood Sampling, Processing and Banking [h] | X | X [f] | |
| Acquisition and banking of multi-region pleural biopsies (4-6) and pleural fluid (100-500ml) for research analyses during LAT or VATS [c, h] | | X | |
| Arrange retrieval of FFPE pleural biopsies from local pathology and transport to RTB [i] | | | X |
| Record Follow-up Data | | X | X |
| Record Adverse Events | | X | X |

a. Not required if VATS thoracoscopy planned
b. A baseline contrast-enhanced CT Thorax should ideally be available within 12 weeks of visit B1 to confirm participant has not progressed since original benign biopsy. If not available, repeat CT should be considered based on clinical judgement but is not mandatory.
c. Please refer to Meso-ORIGINS Biopsy Manual
d. Investigators may introduce the study at earlier clinic visits if eligibility likely and clinically appropriate
e. Participants will be offered a follow-up telephone call with a member of the study team if they wish to have more time to consider the study. This call will occur no later than 2 working days after Visit provision of PIS.
f. If not already performed
g. Including the following baseline blood results from patient records, which should be repeated if not available within 4 weeks of visit B1: full blood count, lactate dehydrogenase, c-reactive protein, albumin, urea and electrolytes. Baseline data also includes results any previous pleural fluid and imaging tests performed as part of routine clinical care.
h. Please refer to Meso-ORIGINS Sample Handling Manual
i. FFPE biopsy blocks should be retrieved from the local pathology archive and transported to the PREDICT-Meso Research Tissue Bank (RTB), based in Glasgow. Please refer to the Meso-ORIGINS Sample Handling Manual for detailed instructions

# 4 INTRODUCTION

## 4.1 BACKGROUND AND AIMS

Malignant Pleural Mesothelioma (MPM) is an invasive thoracic malignancy associated with prior asbestos exposure. It typically develops 30-50 years after asbestos exposure and presents with breathlessness resulting from a pleural effusion. Median survival is generally <1 year, although outcomes are markedly heterogenous[1]. Prognosis is affected by histological subtype, molecular features, age and associated features including weight loss and immune response (systemic and peri-tumoural)[2–4]. Despite recent positive clinical trials, primarily in combination immunotherapy[5], MPM remains universally fatal. With the UK incidence of MPM currently the highest in the world[6] and global death rates rising rapidly (currently 43,000/year)[7,8] there is an urgent need to accelerate research, particularly in relation to target identification and drug development. The PREDICT-Meso International Accelerator Network, and within this, Meso-ORIGINS has been created to address this need.

The MPM tumour genome is dominated by tumour suppressor loss, a low mutational burden and few oncogenic drivers[3,9], posing major challenges for target identification and drug design. However, MPM is preceded by decades of pleural inflammation, providing a window of opportunity for critical target identification and validation. Such an approach is supported by pre-clinical data from PREDICT-Meso members demonstrating epigenomic events that precede MPM evolution in asbestos-dependent animal models[10]. Similar longitudinal studies in humans will facilitate target prioritisation and development of a suite of new pre-clinical models suitable for high-throughput drug screening and validation in downstream PREDICT-Meso work packages.

***The aim of Meso-ORIGINS is to collect matched tissue pairs (benign-MPM) from participants as they evolve from benign pleural inflammation to MPM. The study will also collect non-invasive risk profiling data (blood proteomics, exhaled breath metabolomics, perfusion MRI radiomics), which could be used to select future participants, at a pre-malignant stage, for clinical trials evaluating assets emerging from PREDICT-Meso.***

## 4.2 BENIGN PLEURAL INFLAMMATION AND MPM

MPM is typically presaged by radiological and clinical evidence of chronic, benign pleural inflammation (e.g pleural plaques, pleural thickening) and in some cases, by overt symptomatic pleural effusion, prompting fluid drainage and pleural biopsy on suspicion of MPM. Multiple previous studies report a risk of MPM following detection of benign 'non-specific pleuritis' in the order of 10% over the following 2-years[11–14]. Although cases meeting this description were first described by Eisenstadt in 1965[15], it remains uncertain whether benign pleurisy is genuine precursor to MPM, or simply reflects false negative biopsies in participants with thoracoscopically or otherwise occult MPM. A genuine precursor is certainly plausible since MPM pleural effusion is known to contain numerous pro-angiogenic/pro-tumour/immunosuppressive factors[16,17]. Regardless of whichever is true, this series of events presents a unique window of opportunity to study the last mile of MPM evolution by re-biopsying participants who develop MPM, generating unique benign-MPM pairs from the same individual. Emerging data regarding the clonal evolution[4] and marked spatial (inter-tumour, intra-patient) heterogeneity of MPM[18,19] further supports a discovery strategy that prioritises therapeutic development by integrating biological data from multiple biopsy sites, even if these reflect synchronous sites of benign, pre-invasive and/or invasive MPM.

## 4.3 MESO-ORIGINS FEASIBILITY STUDY

The Meso-ORIGINS Feasibility study was conducted at 4 UK pleural disease centres (Glasgow, Manchester, Oxford, Bristol) and was completed in January 2021. The study addressed important areas of uncertainty regarding the current Meso-ORIGINS design, including the technical feasibility and participant acceptability of a

range of surveillance and repeat biopsy methods and the sample size estimate. The primary objective was to determine whether it would be possible to recruit sufficient numbers of eligible participants to Meso-ORIGINS based on a surveillance protocol involving repeat Local Anaesthetic Thoracoscopy (LAT). This was addressed in the Prospective Arm. The secondary objective was to define the sample size estimate for Meso-ORIGINS more precisely, which was initially estimated at 590 cases. This was addressed in the Retrospective Arm.

The results of the Meso-ORIGINS Feasibility study are summarised in Appendix 1[20]. In brief, using similar eligibility criteria to the current study, the prospective arm recruited 37 eligible participants over 12 months in 4 centres, demonstrating feasibility of the proposed sample size over a large UK network and a recruitment period of 41 months. The retrospective arm observed 42 MPM evolutions in 257 (16% (95%CI 12.3-21.4%)) similar eligible participants. MPM evolution was confirmed histologically by repeat biopsy in 36/257 (14% (95% CI 10.5-19.2)) suggesting that 500 participants (not 590 as originally projected) would need to be recruited here to generate the minimum required number of benign-MPM tissue pairs (n=63), assuming 10% loss to follow up.

### 4.4 TISSUE SAMPLING IN MESOTHELIOMA

Pleural fluid is routinely aspirated to relieve symptoms in participants with MPM and typically contains a mixed cell population, including mesothelial cells and a variety of acute and chronic inflammatory cells[16]. However, the diagnostic yield of pleural fluid cytology is minimal using this material, except in highly selected centres with specialist expertise[21,22]. This reflects the bland cytological appearance of MPM cells, which makes it difficult to differentiate MPM from a benign reactive mesothelial proliferation, even with modern immunocytochemical techniques. Histological confirmation is recommended in all participants where technically possible and safe[23,24]. Thoracoscopy is the optimal biopsy method in suspected MPM, either as Local Anaesthetic Thoracoscopy (LAT) or Video Assisted Thoracoscopic Surgery (VATS). Both techniques allow direct visualisation of the entire pleural surface retrieval of multiple full-thickness biopsies. LAT is well-tolerated, does not require general anaesthesia (GA) and can be performed as a day-case. It offers high diagnostic sensitivity (92.6% n=1369 cases) with a low complication rate (0% mortality in >2000 cases in 28 studies; 1.8% major complication rate in >4500 cases in 47 studies[25]). VATS series report similar outcomes although participants need to be fit for GA.

### 4.5 HETEROGENEITY

MPM is a heterogenous disease clinically, with outcomes varying greatly between apparently similar participants and responses to therapy difficult to predict. Pathologically, MPM is also characterised by considerable intra-tumour heterogeneity (ITH), which may reflect true ITH in a single lesion, the presence of multiple synchronous primary tumours (spatial heterogeneity) and temporal heterogeneity, whereby different regions of asbestos-exposed mesothelium evolving at different rates[4]. These elements will be studied in Meso-ORIGINS, primarily in the Arm B. With regard to spatial heterogeneity, Kiyotani et al reported distinct somatic mutations and immune microenvironment signatures, both between tumours and between participants, based on biopsies collected in 6 participants at 3 different spatial locations (anterior, posterior, diaphragmatic pleura)[19]. Heterogeneity between biopsy sites may reflect classical ITH and the presence of a variable 'within-tumour' neoantigen-related immune response but might also reflect the presence of spatially distinct synchronous primary tumours, each with their own unique somatic mutation and immune signature. Such a thesis is supported by Comertpay et al, who observed a polyclonal origin in 14 out of 15 MPM tumour biopsies, based on human androgen receptor assays (HUMARA)[18]. It is also plausible that different sites on the pleural mesothelium will respond at different rates (or not at all) to asbestos dosing, depending on local factors (e.g., dose received, environmental pressures, such as tissue oxygenation, pH and perfusion) which vary greatly across the surface area of the pleura (which measures 40 $m^2$ in an average 70 kg male)[26]. In asbestos-driven mouse models of MPM, invasive tumour is preceded by macrophage-mediated chronic inflammation (frustrated phagocytosis)[27] and epigenomic events such as CDKN2A hypermethylation[10]. In human participants, chronic inflammation, pre-invasive molecular

events (including CDKN2A hemi-/homozygous loss and BAP1 loss) and invasive MPM frequently co-exist in the same patient in different biopsies. This is frequently observed in MDT discussion of thoracoscopic sampling, during which 4-10 biopsies are typically acquired from across the pleural surface. This suggests the presence of *simultaneous but not synchronous* events, which may all have the potential to evolve into invasive MPM. Such a thesis is supported by increasing MPM risk with increasing latency from exposure[28], which differs from other environmental cancers, e.g., lung cancer, where risk decreases following smoking cessation. A better understanding of inter- and intra-patient and intra-tumour heterogeneity is critical to the development of more effective MPM therapies.

## 4.6 NON-INVASIVE TOOLS FOR DETECTION OF MPM

Contrast-enhanced computed tomography (CT) is used routinely for diagnosis and monitoring of both confirmed MPM and surveillance following a diagnosis of benign asbestos-associated pleural disease. In MPM, typical morphological features include pleural thickening (classically >1cm, nodular or affecting the mediastinal pleura), fissural nodularity and infiltration of the chest wall or diaphragm[29,30]. However, these are non-specific and insensitive, with approximately 40% participants having a 'benign' CT, with only pleural effusion visible at diagnosis[31]. Magnetic resonance imaging (MRI) offers superior sensitivity, especially when combined with perfusion studies, but is less familiar to clinical radiologists and not available in every centre. Perfusion MRI can identify the earliest stages of MPM with >90% sensitivity and specificity and appears particularly useful in participants with only minimal pleural thickening[32]. Thoracic ultrasound (TUS) is not used as diagnostic test *per se* but is a critical tool for decision-making re LAT feasibility. TUS may identify tumour nodules, fluid septation and the presence/absence of normal 'lung sliding', where the latter infers LAT feasibility[33]. When lung sliding is absent, TUS may also identify a tumour nodule that can be targeted by bedside US or CT as an alternative[34].

Blood tests for MPM have been studied widely over recent decades but no marker provides sufficient sensitivity at high specificity. However, in a recently reported prospective study (n=749), the SOMAscan® proteomic assay reliably differentiated MPM from asbestos exposed controls (75% sensitivity, 88% specificity, validation cohort AUC 0.855). Exhaled Breath metabolomics are an alternative non-invasive test for MPM, but these have yet to be prospectively validated. In the Mesobreath studies, a breath signature based on gas chromatography-mass spectrometry discriminated MPM from asbestos-exposed subjects with 100% sensitivity & 91% specificity[35–37]. These non-invasive tools will all be deployed in Meso-ORIGINS, either for routine surveillance and diagnosis of MPM (CT), biopsy planning (TUS) or a risk-profiling inputs for MPM evolution (serum proteomics, exhaled breath metabolomics, perfusion MRI). None of the risk-profiling inputs will be used for diagnostic purpose. Therefore, these results will not be presented to clinical teams or patients.

## 4.7 STUDY RATIONALE

Meso-ORIGINS will generate a large cohort of paired tissue samples from participants with asbestos-associated benign pleural inflammation. This will include participants who progress to MPM (**Benign-MPM Evolution pairs**) and those who do not after at least 18-months of reassuring follow-up (**Benign-No MPM evolution pairs**). The tissue pairs collected will be subject to multiomic molecular characterisation in downstream PREDICT-Meso work-packages and will be used to generate a suite of new pre-clinical MPM models, for high-throughput drug screening and target-drug validation. The study design is based on the results of the Meso-ORIGINS Feasibility Study (see Appendix 1).

# 5 STUDY OBJECTIVES

## 5.1 PRIMARY OBJECTIVE

- To create a prospective cohort of participants with asbestos-associated benign pleural inflammation, of whom an estimated 63 participants will develop MPM within 2 years of recruitment

## 5.2 SECONDARY OBJECTIVES

- To generate a risk prediction model for evolution of MPM within 2 years, based on radiomic, proteomic, metabolomic inputs
- To collect spatially distinct tumour biopsies from participants with MPM, facilitating comprehensive characterisation of intra-patient tumour heterogeneity.

# 6 STUDY DESIGN

Meso-ORIGINS is a multi-centre prospective observational study, incorporating two arms (A and B) and an MRI sub-study within Arm A.

## 6.1 STUDY POPULATION

### 6.1.1 Arm A

Arm A will prospectively recruit 500 asbestos-exposed participants with evidence of associated **benign** pleural disease, based on an initial pleural tissue biopsy (of any form) within the last 1 year. Recruitment will be via a large UK network of pleural centres over a 41-month period. Importantly, a persisting clinical suspicion of MPM after an initial benign pleural biopsy is NOT an exclusion criterion and such participants should be recruited, even if immediate re-biopsy is planned. This includes participants with malignant-looking CT imaging (e.g., pleural thickening >1cm, pleural nodules, fissural nodules). All participants will have baseline data recorded, their initial biopsies banked and non-invasive risk-profiling samples (blood, exhaled breath +/- MRI in participating centres). All will be subject to regular follow-up over a subsequent 2-year period. **If MPM is suspected at any time following registration the participant will have repeat biopsies as directed by the local clinical team, with research banking of tissue samples.** A proportion of participants with benign follow-up will also be invited to have repeat biopsies purely for research purposes, if this is technically feasible based on TUS. Based on the results of the Meso-ORIGINS feasibility study, and assuming 10% loss to follow-up, we estimate that 63 (14% (95% CI 10.5-19.2) participants will have MPM confirmed histologically over the 2-year study follow-up period. Notably, the median time to MPM evolution in the feasibility study was 5.8 months.

#### 6.1.1.1 MRI Sub-study

The MRI sub-study will recruit 100 participants from Arm A (50% of the predicted recruitment at participating sites). This sample size reflects the availability of research MRI in the UK pleural disease network, based on experience in recent studies and is expected to generate approximately 12 cases of MPM.

### 6.1.2 Arm B

Arm B will recruit 250 eligible participants prior to either LAT or VATS thoracoscopy. It is expected cases will be identified via urgent suspicion of cancer (USOC)/2-week wait urgent referral pathways. Multi-region research biopsies will be acquired during LAT/VATS in all cases, in addition to blood sampling (germline, whole blood, serum and plasma). 250 cases should generate at least 91 cases of histologically confirmed MPM, (based on prior data[22]) and approximately 107 cases with benign pleural inflammation (based on interim review of Arm B numbers early in 2023). This will provide abundant material for downstream heterogeneity analyses including interrogation of benign biopsies in patients who transition to Arm A (which is permitted but not mandatory).

Transition to Arm A will facilitate linkage of pre-MPM multi-region biopsies with subsequent MPM evolution and will require additional Arm A consent. Arm B participants with confirmed MPM may be directed to the ASSESS-Meso study (a sister study within PREDICT-Meso) at sites where this is recruiting. This involves longitudinal follow-up post-MPM, maximising project impact.

## 6.2 ELIGIBILITY CRITERIA

### 6.2.1 Arm A

All participants will be subject to the following eligibility criteria. All inclusion criteria and no exclusion criteria must be met. Queries related to eligibility should be addressed with the PREDICT-Meso Project Manager (PM) prior to study registration.

**Inclusion Criteria**

- History of asbestos exposure or imaging compatible with this (e.g., pleural plaques)
- Any form of pleural tissue biopsy within last 1 year showing evidence of associated pleural inflammation (e.g., benign fibrinous pleurisy, non-specific pleuritis, atypical mesothelial proliferation, mesothelioma in situ)
- ≥16 years of age
- Informed written consent to at least banking of any previous and future pleural tissue samples

**Exclusion Criteria**

- Any cytologically or histologically confirmed pleural malignancy*
- Any pleural infection including TB
- Granulomatous pleural inflammation
- Any specific pleuritis diagnosed (e.g., Rheumatoid Arthritis (RA) Pleurisy)
- Previous Pleurodesis

* A persisting clinical suspicion of MPM after an initial benign pleural biopsy is NOT an exclusion criterion and such participants should be recruited, even if immediate re-biopsy is planned

#### 6.2.1.1 Arm A – MRI sub-study

Only participants recruited to Arm A at centres participating in the MRI sub-study will be eligible, based on the following criteria:

**Inclusion Criteria**

- Registered to Arm A
- Informed Written Consent to participation in the MRI sub-study

**Exclusion Criteria**

- Any contraindication to MRI, e.g., claustrophobia, pregnancy, metallic foreign body, pacemaker or ferrous metal implant, unable to lie flat
- Allergy to Gadolinium contrast
- Significant renal impairment (defined as eGFR <30 ml/min)

### 6.2.2 Arm B

All participants will be subject to the following eligibility criteria. All inclusion criteria and no exclusion criteria must be met. Queries related to eligibility should be addressed with the PREDICT-Meso Project PM prior to study registration.

**Inclusion Criteria**

- Suspected pleural malignancy, as defined by a unilateral pleural effusion or pleural-based mass lesion
- History of asbestos exposure or typical radiological features, e.g., pleural plaques
- Sufficient fitness for thoracoscopy (LAT or VATS are permissible)
- ≥16 years of age
- Informed written consent

**Exclusion Criteria**

- Current or recent (within last 3 months) intercostal chest drain
- Previous Pleurodesis

## 6.3 IDENTIFICATION OF PARTICIPANTS AND CONSENT

### 6.3.1 Arm A

Participants will be identified via clinics, inpatient reviews, and MDT meetings. Potentially eligible participants can be approached and provided with a participant information sheet (PIS) at any time and will be given sufficient time, in their own judgement, to consider participation. Same-day consent is permissible in participants who are comfortable with this, since recruitment opportunities may be infrequent, with routine clinic reviews typically occurring every 6 months. However, if participants would like more time to consider involvement, a follow-up telephone call with a member of the study team will be offered and will occur no later than 2 working days after provision of PIS. All participants will be made aware that participation is voluntary, and that they may decline or withdraw at any time without their care being affected. Eligibility will be confirmed by a doctor.

#### 6.3.1.1 Arm A: MRI sub-study

Participants will be recruited from within Arm A at MRI sub-study participating centres only. Potentially eligible participants will be identified during Visit A1, at which time an additional MRI sub-study PIS will be provided, and participants will be given sufficient time, in their own judgement, to consider participation. Documentation of additional consent on a separate form is required. As in the main arm, a telephone call will be offered within 2 working days if participants require more time and participants will be made fully aware that participation is voluntary, and they can withdraw at any time. Potential participants will be advised that involvement in the sub-study is not mandatory for Arm A and that this is an additional, voluntary element. Eligibility will be confirmed by a doctor.

### 6.3.2 Arm B

Participants will be identified via clinics, inpatient reviews, and MDT meetings. Potentially eligible participants can be approached the same time as diagnostic thoracoscopy scheduling. However, the study can be introduced at earlier clinic visits if eligibility is likely, and this discussion is clinically appropriate. When the study is introduced, a PIS will be provided, and the participant will be given sufficient time (in their own judgement) to consider participation. Same-day consent is permissible in participants who are comfortable with this given the rapid nature of diagnostic cancer pathways. However, a follow-up telephone call will be offered within 2 working days if participants require more time and participants will be made fully aware that participation is voluntary, and they can withdraw at any time. Eligibility will be confirmed by a doctor.

## 6.4 REGISTRATION

Participants cannot be registered until the site has been activated. All participants must be screened and registered onto the study prior to commencement of any study activity. Separate eligibility/registration forms

are provided to allow eligibility confirmation by the site PI (or delegate) prior to patient attendance and registration (which can be performed by research nursing staff). To register a participant to Arm A, the Arm A MRI sub-study or Arm B, please contact the CRUK Glasgow Clinical Trials Unit (CTU) as follows:

| |
|---|
| **☎: 0141 301 7952** |
| ggc.recruitment.crukglasgowctu@nhs.scot |
| **CTU Opening Hours:** 08.30-17.00 Mon-Thu, Fri 08.30-16.30, except public holidays |
| If registration is urgent, please call instead of emailing |

The participant's eligibility criteria will be checked and, if eligible, a study number will be allocated at this point. All participants must be screened and registered onto the study prior to commencement of any study activity. With the participant's consent, their GP will be informed of their involvement in the study.

### 6.5 REMOTE OBSERVATION

Participants who decline follow up visits can consent to remote observation. This will provide consent to retrieve and bank previous pleural tissue samples and any subsequent samples taken on suspicion of MPM Evolution. Such participants may sign a consent form as normal (with site staff in person), or use the remote consent process, if this is more convenient for the participant, see Section 19.2 for further details.

### 6.6 WITHDRAWAL OF PARTICIPANTS FROM THE STUDY

Participants have the right to withdraw at any point for any reason. Similarly, the investigator may withdraw participants in the event of an intercurrent illness, the participant no longer being fit for study procedures, Adverse Events (AEs), Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reaction (SUSARs), protocol violations or any other relevant reason. If a participant withdraws from the study, it should be clearly documented in the participant's notes what they are withdrawing from (consent to use any past data, consent to use any samples collected or consent for further data collection). If a participant withdraws their consent, the site must contact the CTU with full details of the withdrawal. Where applicable, the CTU may ask the site to complete a Consent Withdrawal Form. On this form, option A ensures maximum utilisation of the data, samples and contribution made, and is the preferred option, if acceptable to the participant.

### 6.7 CO-ENROLMENT GUIDELINES

If sites wish to recruit participants to any interventional studies, the Sponsor and Study Management Group (SMG) will consider this on a study-by-study basis and where required request ethical approval to allow co-enrolment. It is imperative that the Sponsor of the other study is also contacted and approves co-enrolment within their study.

## 7 STUDY ENDPOINTS

### 7.1 PRIMARY ENDPOINT

The primary endpoint shall be the number of participants in Arm A diagnosed with MPM at any point from study registration to completion of 2 years follow-up.

### 7.2 SECONDARY ENDPOINTS

- Results of a multiomic risk classifier for MPM evolution within 2-years based on radiomic, proteomic and metabolic measurements in participants at baseline in Arm A
- Number of participants in Arm B with histologically confirmed MPM following thoracoscopy

# 8 STUDY ACTIVITIES: ARM A

## 8.1 VISIT A1: BASELINE (DAY 1)

Visit A1 activities should ideally be completed on the same day, but can be completed over up to 14 days, following provision of PIS. This allows additional time to consider participation, and flexibility at site for translational sampling. If patients decline participation, this should be recorded on the local screening fail log.

**Routine Clinical Activity**

- Clinical review: likely to be in an outpatient clinic but may be in any appropriate clinical setting. Focused on symptoms, any recent imaging, pleural fluid and tissue biopsy results and probable diagnosis
- A baseline contrast-enhanced CT Thorax should ideally be available within 12 weeks of visit A1 to confirm participant has not progressed since original benign biopsy. If not available, repeat CT should be considered based on clinical judgement but is not mandatory
- Arrange repeat pleural biopsy (and fluid sampling if available) if clinically indicated (suspected MPM Evolution). The method used is at the discretion of the clinician in charge, but LAT sampling is preferred when feasible. At baseline this will only be suitable for participants in whom there is strong persisting suspicion of MPM despite negative (benign) pleural biopsies from a recent procedure

**Arm A Study Activity**

- Review Eligibility Criteria
- Introduce study and provide with Arm A PIS if potentially eligible. **NB:** Investigators may introduce the study at earlier clinic visits (including remote visits), and post/email the PIS out following this, if clinically appropriate. Eligibility can then be confirmed at subsequent face-to-face visit.
- Discussion and Informed Written Consent*
- Register participant with CTU
- Record Baseline Data from patient records, including bloods (which should be repeated if not available within 4 weeks of visit A1) & any pleural fluid, biopsy & imaging tests
- Research blood samples (germline, whole blood, plasma and serum) taken, processed and banked**
- Research exhaled breath samples collected and processed ***
- Bank pleural fluid sample if patient has an IPC in-situ. It is acknowledged that not all patients will have an IPC. Pleural fluid samples require immediate processing and storage**
- Arrange retrieval of the FFPE pleural biopsies on which the diagnosis of benign pleural inflammation has been made from the local pathology archive. These should be transported to the PREDICT-Meso Research Tissue Bank (RTB), based in Glasgow**
- Record Adverse Events

* Participants may choose to defer consent if they required additional time to consider involvement, in which case a follow-up telephone call will be offered no later than 2 working days after provision of PIS. Consent to the main study, registration, baseline data collection and blood and breath sample collection must then occur during a further attendance within 14 days of PIS provision, or at Visit A2 at sites participating in the MRI sub-study.

** Please refer to the Meso-ORIGINS Sample Handling Manual

*** Please refer to Meso-ORIGINS Exhaled Breath Sampling Manual. Exhaled breath samples can be omitted at sites where facilities are not in place for acquisition or storage, or on grounds of patient preference

**MRI Sub-study Activity (participating sites only)**

- Review Eligibility Criteria
- Introduce sub-study and provide with separate sub-study PIS if potentially eligible
- Discussion and Informed written consent***
- Register participant with CTU* above

*** Consent and registration to the MRI sub-study can be documented at Visit A2 if the participant would like more time to consider participation.

## 8.2 VISIT A2: MRI (DAY 15 ± 10 DAYS)

Visit A2 is only applicable to the MRI sub-study and should therefore be omitted at sites not participating in this. For participating sites, A2 affords a second opportunity for uncompleted A1 activities. This can include recording of consent and study registration in participants who require additional time to consider their involvement.

**Routine Clinical Activity**

- None

**Arm A Study Activity**

The following can all be undertaken if not completed at Visit A1, but do not need to be repeated:

- Discussion and Informed Written Consent
- Register participant with CTU
- Record Baseline Data from patient records, including blood results (which should be repeated if not available within 4 weeks of visit A1) & any pleural fluid, tissue biopsy and imaging tests
- Research blood samples (whole blood, plasma and serum) taken, processed and banked*
- Research exhaled breath samples collected and processed**
- Record Adverse Events

* Please refer to the Meso-ORIGINS Sample Handling Manual

** Please refer to Meso-ORIGINS Exhaled Breath Sampling Manual. Exhaled breath samples can be omitted at sites where facilities are not in place for acquisition or storage, or on grounds of patient preference

**MRI Sub-study Activity**

- Informed written consent to sub-study *(if not already performed at Visit A1)*
- Register participant for MRI sub-study with CTU *(if not already performed at Visit A1)*
- MRI Safety Questionnaire
- Orbital Radiograph if indicated by relevant history to exclude a metallic foreign body
- Contrast-enhanced MRI Thorax**
- Record Adverse Events

** Please refer to the Meso-ORIGINS MRI Manual

## 8.3 VISIT A3: FOLLOW-UP #1 (6 MONTHS ± 4 WEEKS)

**Routine Clinical Activity**

- Clinical review to assess for potential MPM evolution
- Contrast-enhanced CT Thorax: advisory within 6 weeks of visit date
- Arrange repeat pleural biopsy (and fluid sampling if available) if clinically indicated (suspected MPM Evolution). The method used is at the discretion of the clinician in charge, but LAT sampling is preferred when feasible. When not feasible, image-guided biopsy is acceptable.

**Arm A Study Activity**

- Record follow-up clinical data
- Research blood samples (whole blood, plasma and serum) taken, processed and banked*
- Record any adverse events

* Please refer to the Meso-ORIGINS Sample Handling Manual

## 8.4 VISIT A4: FOLLOW-UP #2 (12 MONTHS ± 4 WEEKS)

**Routine Clinical Activity**

- Clinical review to assess for potential MPM evolution
- Contrast-enhanced CT Thorax: advisory within 6 weeks of visit date
- Arrange repeat pleural biopsy (and fluid sampling if available) if clinically indicated (suspected MPM Evolution). The method used is at the discretion of the clinician in charge, but LAT sampling is preferred when feasible. When not feasible, image-guided biopsy is acceptable

**Arm A Study Activity**

- Record follow-up clinical data
- Research blood samples (whole blood, plasma and serum) taken, processed and banked*
- Record any adverse events

* Please refer to the Meso-ORIGINS Sample Handling Manual

## 8.5 VISIT A5: FOLLOW-UP #3 (18 MONTHS ± 4 WEEKS):

**Routine Clinical Activity**

- Clinical review to assess for potential MPM evolution
- Contrast-enhanced CT Thorax: advisory within 6 weeks of visit date
- Arrange repeat pleural biopsy (and fluid sampling if available) if clinically indicated (suspected MPM Evolution). The method used is at the discretion of the clinician in charge, but LAT sampling is preferred when feasible. When not feasible, image-guided biopsy is acceptable

**Arm A Study Activity**

- Record follow-up clinical data
- Research blood samples (whole blood, plasma and serum) taken, processed and banked*
- Record any adverse events
- Discuss possibility of repeat biopsy if NO CLINICAL SUSPICION OF MESOTHELIOMA
- If a repeat biopsy is potentially acceptable to the participant and appears feasible, immediately screen by TUS** or arrange a formal screening visit (see Visit A7)

* Please refer to the Meso-ORIGINS Sample Handling Manual

** Please refer to the Meso-ORIGINS Ultrasound Manual. TUS assessment focused on technical feasibility of LAT, and if LAT not feasible, the feasibility of image guided biopsy (US or CT)

## 8.6 VISIT A6: FOLLOW-UP #4 (24 MONTHS ± 4 WEEKS)

**Routine Clinical Activity**

- Clinical review to assess for potential MPM evolution
- Contrast-enhanced CT Thorax: advisory within 6 weeks of visit date
- Arrange repeat pleural biopsy (and fluid sampling if available) if clinically indicated (suspected MPM Evolution). The method used is at the discretion of the clinician in charge, but LAT sampling is preferred when feasible. When not feasible, image-guided biopsy is acceptable

**Arm A Study Activity**

- Record follow-up clinical data
- Research blood samples (whole blood, plasma and serum) taken, processed and banked*
- Record any adverse events
- Discuss possibility of repeat biopsy if NO CLINICAL SUSPICION OF MESOTHELIOMA
- If a repeat biopsy is potentially acceptable to the participant and appears feasible, immediately screen by TUS** or arrange a formal screening visit (see Visit A7)

* Please refer to the Meso-ORIGINS Sample Handling Manual

** Please refer to the Meso-ORIGINS Ultrasound Manual

**Visits A7, A8 and A9** are only relevant to participants in whom there is **NO CLINICAL SUSPICION OF MESOTHELIOMA** after at least 18 months of follow-up, and in whom the research team feel a repeat biopsy *might* be feasible. They can be omitted if repeat biopsy of any form would clearly not be acceptable based on earlier discussions, or the site PI judges that repeat biopsy is clearly not feasible or would involve higher than normal risk. **Where possible, these visits should be conducted in all other suitable patients.**

## 8.7 VISIT A7: REPEAT BIOPSY SCREENING (UP TO 4 WEEKS FOLLOWING VISIT A5 *or* A6)

**Routine Clinical Activity**

- None

**Arm A Study Activity**

- TUS assessment* focused on technical feasibility of LAT, and if LAT not feasible of image guided biopsy
- Record technical feasibility assessment
- Arrange date for LAT or image-guided biopsy, if judged technically feasible and acceptable to participant
- Record follow-up data
- Record any adverse events

* Please refer to the Meso-ORIGINS Ultrasound Manual

## 8.8 VISIT A8: REPEAT BIOPSY (UP TO 2 WEEKS FOLLOWING TUS SCREENING)

**Routine Clinical Activity**

- None

**Arm A Study Activity**

- Repeat biopsy and pleural fluid sampling, ideally by LAT or image guided biopsy**. It is acknowledged that fluid sampling may not be possible if LAT is not feasible, and image guided biopsies are required. If fluid can be sampled, immediate processing and storage is required***. Biopsies are handled as per normal local pathology processes with later retrieval of FFPE pleural biopsy blocks (see Visit A9)
- Chest radiograph (within 1-12 hours following biopsy)
- Record follow-up data
- Record any adverse events

** Please refer to the Meso-ORIGINS Biopsy

*** Please refer to the Meso-ORIGINS Sampling Handling Manual

## 8.9 VISIT A9: POST-REPEAT BIOPSY (UP TO 2 WEEKS POST-VISIT A8)

**Routine Clinical Activity**

- None

**Arm A Study Activity**

- Review and discuss results of repeat biopsy
- Arrange retrieval of FFPE pleural biopsy blocks from the local pathology archive and transport to the PREDICT-Meso Research Tissue Bank (RTB) in Glasgow****
- Record follow-up data
- Record any adverse events

**** Please refer to the Meso-ORIGINS Sample Handling Manual

# 9 STUDY ACTIVITIES: ARM A REMOTE OBSERVATION

Remote observation participants are, by definition, not required to attend study visits but it is essential that site teams establish a system for remote surveillance, e.g., using electronic heath records and/or via liaison with the clinical team. Remote monitoring should be sufficiently regular to ensure any repeat pleural biopsies, performed during routine clinical follow-up, can be retrieved promptly. A remote observation surveillance form should be completed at least every 6 months following registration to align with participants in Arm A attending study visits. A form should also be submitted immediately on notification or observation of repeat pleural biopsies being performed at any other time.

# 10 STUDY ACTIVITES: ARM B

## 10.1 VISIT B1: BASELINE (DAY 1)

Visit B1 activities should ideally be completed on the same day but can be completed over up to 7 days following provision of PIS to allow participants additional time to consider participation. If patients decline participation, this should be recorded on the local screening fail log.

**Routine Clinical Activity**

- Clinical review: likely to be in an outpatient clinic but may be in any appropriate clinical setting. Focused on symptoms, recent imaging and clinical suspicion of pleural malignancy including Mesothelioma.
- TUS assessment of technical feasibility of LAT (not required if plan is for VATS thoracoscopy)
- A baseline contrast-enhanced CT Thorax should ideally be available within 12 weeks of visit B1. If not available, repeat CT should be considered based on clinical judgement but is not mandatory
- Arrange thoracoscopy (LAT or VATS are both acceptable).

**Arm B Study Activity**

- Review Eligibility Criteria
- If potentially eligible, introduce study and provide with Arm B PIS. **NB:** Investigators may introduce the study at earlier visits (including remote visits), and post/email the PIS out following this, if clinically appropriate. Eligibility can then be confirmed at subsequent face-to-face visit.
- Discussion and Informed Written Consent *
- Register participant with CTU
- Record Baseline Data from patient records, including bloods (which should be repeated if not available within 4 weeks of visit B1) & any pleural fluid and imaging tests
- Research blood samples taken (germline, whole blood, plasma and serum), processed and banked**

* Participants may choose to defer consent if they required additional time to consider involvement. Participants will therefore be offered a follow-up telephone call with a member of the study team no later than 2 working days after provision of PIS. Consent to Arm B, registration and baseline data collection must then occur during a further attendance which must be within 7 days of Visit B1, or at Visit B2.

** Please refer to the Meso-ORIGINS Sample Handling manual

## 10.2 VISIT B2: THORACOSCOPY (DAY 15 ± 14 DAYS)

**Routine Clinical Activity**

- Thoracoscopy (LAT or VATS) with pleural biopsies and fluid sent for diagnostic purposes*
- Chest radiograph (within 1-12 hours of procedure)

**Arm B Study Activity**

- Discussion and Informed Written Consent (*if not already completed at Visit B1)*
- Register participant with CTU *(if not already completed at Visit B1)*

- Record Baseline Data *(if not already completed at Visit B1)*
- Research blood samples taken, processed and banked *(if not already completed at Visit B1)***
- Acquisition and banking of multi-region pleural biopsies (4-6) and pleural fluid (100-500ml) for research*

* Please refer to the Meso-ORIGINS Biopsy and Sample Handling Manuals
** Please refer to the Meso-ORIGINS Sample Handling manual

### 10.3 VISIT B3: POST-THORACOSCOPY (DAY 29 ± 14 DAYS)

**Routine Clinical Activity**

- Clinical review with results of pleural sampling

**Arm B Study Activity**

- Arrange retrieval of research specific FFPE pleural biopsies from local pathology and transport to PREDICT-Meso Research Tissue Bank (RTB) in Glasgow*
- Record follow-up data
- Record Adverse Events
- If diagnosis made of asbestos-associated benign pleural disease, consider eligibility for Arm A
- If diagnosis made of Mesothelioma, consider eligibility for ASSESS-Meso study, if this is open in the recruiting centre (ASSESS-Meso is part of WP5 in the PREDICT-Meso Accelerator).

* Please refer to the Meso-ORIGINS Sample Handling Manual

## 11 LABORATORY TESTS

Blood samples will be drawn at Baseline (Visits A1 And B1) and at all Follow-ups in Arm A (#1-4, Visits A3-A6). At sites participating in the MRI sub-study, baseline bloods can also be drawn at the MRI Visit (A2), if these were not collected at Visit A1. Immediate processing should occur at each study centre and detailed instructions for sample collection and processing are provided in the Meso-ORIGINS Sample Handling Manual. Consumables supplied by the lead centre are listed in this document, including PAXgene tubes for collection of germline DNA. All samples will be labelled with a unique Study Number and stored in a -80 Freezer within 2 hours. Arrangements for the collection of blood samples from each centre will be coordinated by the lead centre. Breath samples will be drawn at Baseline (Visit A1) only, but like blood samples can also be collected at the MRI Visit (A2), if not collected at Visit A1 at sites participating in the MRI sub-study. Detailed instructions for breath sample collection and processing are provided in the Meso-ORIGINS Exhaled Breath Sampling Manual. Exhaled breath samples can be omitted at sites where facilities are not in place for acquisition or storage, or on grounds of patient preference. Relevant consumables supplied by the lead centre are listed the Exhaled Breath Sampling Manual. All samples will be labelled with a unique Study Number. Arrangements for the collection of breath samples from each centre will be coordinated by the lead centre.

## 12 PLEURAL BIOPSY RETRIEVAL AND RETURN

The retrieval, banking and analysis of previously acquired and subsequent biopsy material is a key component of Meso-ORIGINS and directly supplies downstream work packages in the PREDICT-Meso Accelerator Network.

- Study teams at site are therefore required to arrange retrieval and transport of the formalin-fixed paraffin embedded (FFPE) pleural biopsies on which the diagnosis of BENIGN PLEURAL INFLAMMATION has been made. This process should be initiated at Visit A1 (or A2 at sites participating in the MRI sub-study) and consider part of that visit's activities. This also applies to patients within the Remote Observation Arm.

- The same retrieval process must be initiated immediately following repeat biopsy sampling in patients with CLINICAL SUSPICION OF MESOTHELIOMA. Since this event may occur at any point following recruitment, systems must be established locally to ensure research teams are aware of such events.
- FFPE biopsy retrieval must also be initiated after repeat pleural biopsies in patients with NO CLINICAL SUSPICION OF MESOTHELIOMA at Visit A9, when this pathway is followed for study participants.
- Teams are also required to retrieve and arranged transport for the research specific FFPE biopsies acquired in Arm B as part of Visit B3.
- See Meso-ORIGINS Sample Handling Manual for detailed labelling instructions for the above

These samples will then be transported to Glasgow and stored securely in the PREDICT-Meso Research Tissue Bank, which is a satellite tissue bank of NHS GGC Biorepository. The RTB has been created for this purpose and has received REC approval for this function (Ref: 21/WS/0011). Samples will be stored, without any additional analysis or DNA/RNA extraction unless this is required for associated research. **NB:** Pleural fluid samples should also be acquired, processing and banked where possible during follow-up biopsy procedures. It is acknowledged this may not be feasible when image-guided biopsy techniques are used. Unlike biopsies, fluid samples require immediate processing by the research team; specific guidance is provided in the Sample Handling Manual.

### 12.1 SAMPLE RETURN PROCESS

Occasionally, site local pathology departments may wish to review pleural biopsies transferred from their own archive to the PREDICT-Meso RTB, e.g., following a subsequent biopsy or as part of a medico-legal claim for compensation or as part of a subsequent trial. A dedicated process is available for this purpose, guaranteeing return to sites within 5 working days of request. To request return of samples, contact the PREDICT-Meso Project PM (Alexandrea.macpherson@glasgow.ac.uk), noting the Site Registration Number and Meso-ORIGINS sample number (see Tumour block transfer Form). Every effort will be made to minimise block disruption and retain block integrity. A courier will be organised for this purpose by the NHS GGC Biorepository.

## 13 ASSESSMENT OF SAFETY

### 13.1 LAT AND VATS

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, in participants with symptomatic pleural effusion. In this clinical setting, LAT is well-tolerated and can be performed as a day-case[25]. It offers high diagnostic sensitivity (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)[38]. Video assisted thoracoscopic surgery (VATS) offers similar high diagnostic sensitivity to LAT is also safe with a low complication rate. However, the procedure requires general anaesthesia, intubation and single lung ventilation and is therefore not suitable for participants with major comorbidities. In one large series (n=566), the most common side effect was subcutaneous emphysema with cardiac dysrhythmia and air embolism occurring in <1% and no deaths[39].

### 13.2 CONTRAST-ENHANCED MRI (FOR MRI SUB-STUDY)

MRI is a safe procedure and no ionising radiation is involved. Participants will only be asked to attend for an MRI scan if clinically stable and able to lie flat comfortably. Gadolinium contrast (e.g., Gadovist™) will be administered through an intravenous cannula during the procedure, at a dose of 0.05 mmol/kg. Gadolinium is well tolerated by the vast majority of participants and licensed for this purpose. The frequency of adverse events after an injection of 0.1 to 0.2 mmol/kg of gadolinium ranges from 0.07% to 2.4%. The majority of these adverse reactions

are mild. Anaphylactoid reactions are extremely rare (0.001% to 0.01%). All scans will be performed with continuous electrocardiograph (ECG) monitoring, regular blood pressure (BP) and facilities for oxygen saturations measurements available. The scan will be carried out under the supervision of a physician with training in Adult life support (ALS). Within the MRI units involved, a regularly maintained resuscitation trolley with defibrillator, oxygen and drugs will be immediately available in the unlikely occurrence of an adverse event (AE). Participants will be monitored for a minimum of 30 minutes post administration of contrast.

# 14 SAFETY REPORTING

Only Adverse Events (AEs) and Serious Adverse Events (SAEs) thought to be related to study procedures require recording and reporting. Specifically, this includes AEs associated with venous blood sampling, exhaled breath sampling, chest radiographs, LAT, VATS or image-guided pleural biopsy. For participants in the MRI sub-study, only AEs and SAEs thought to be related to the MRI acquisition, including administration of gadolinium contrast, and the x-ray of orbits (if acquired) require to be recorded and reported. Safety reporting will be performed by the Pharmacovigilance Department of the CRUK Glasgow CTU as delegated by the study Sponsor. These definitions apply to all study participants from study Visit 1.

## 14.1 DEFINITIONS

As all baseline study related procedures at visit A1 and B1 are routine and non-invasive, the risk of AEs and SAEs has been assessed as low. Therefore, AEs and SAEs only need reported from visit A2 and B2 up to and including 180 days after the last procedure.

| Term | Definition |
|---|---|
| **Adverse Event (AE)** | An adverse event (AE) is any untoward medical occurrence in a study participant, which may not have a causal relationship with any study procedure. |
| **Related Adverse Event (RAE)** | A related adverse event (RAE) is any AE which is thought to be caused by or related to the study procedure or intervention. |
| **Term** | **Definition** |
| **Serious Adverse Event (SAE)** | A serious adverse event (SAE) is any AE associated with any of the following, whether or not considered related to the study procedure or intervention.<br>• inpatient hospitalisation or prolongation of existing hospitalisation*<br>• persistent/significant disability or incapacity<br>• congenital anomaly/birth defect<br>• life-threatening (at the time of the event) ** or results in death<br>• considered medically significant by the Investigator***<br>* should be defined as a hospital admission required for treatment of an AE. No time frame is specified for the duration of the admission. Referral or transfer to hospice care for normal disease management procedures are not considered a hospitalisation.<br>**the participant was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.<br>*** These are events that may not result in death, are not life threatening, or do not require hospitalisation, but may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Medical and scientific judgement should be exercised in deciding whether an event is “serious” in accordance with this criterion. |

**NB:** To avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event (for example Common Terminology Criteria for Adverse Events (CTCAE) grade), which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

## 14.2 DETECTING, RECORDING AND REPORTING OF ADVERSE EVENTS

Sites must always record all AEs in the participant's notes even though they are not required to be recorded in the electronic Case Report Form (eCRF). When investigators record AEs in the participant's notes, they should record the severity (CTCAE grade), seriousness and causality (relationship of the AE to the study procedure).

### 14.2.1 Detection of Adverse Events

Participants will be asked at each study visit about the occurrence of AEs since their last visit. AEs will be recorded, notified, assessed, reported, analysed and managed in accordance with the Health Research Authority (HRA) requirements. AEs must be recorded as they are reported whether spontaneously volunteered or in response to questioning about well-being at study visits. The questioning about AEs will cover the current visit as well as the period of time between the previous and the current visit. All AEs must be documented in full in the participant's medical records whether they are required to be recorded in the CRF or not.

### 14.2.2 Recording of Adverse Events

Full details of AEs including the nature of the event, start/stop dates, severity (CTCAE grade), seriousness and causality (relationship to the study intervention) and outcome will be recorded in the participant's medical records and in the study MACRO system as required. AEs must be reported from Visit 1 and followed until:

- They resolve
- If present at pre-study procedure, until the AE returns to the CTCAE grade observed at pre-procedure
- The AE is confirmed as unlikely to ever resolve

If none of the criteria above are met by 180 days following the last study procedure, the AE no longer requires to be followed up. An exacerbation of a pre-existing condition is an AE. The Investigator does not need to actively monitor participants for AEs once the study has ended, unless required.

### 14.2.3 Assessment of Adverse Events

All AEs and must be coded and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. These criteria can be accessed via the NCI Website. AEs must be assessed for seriousness, causality and severity. This assessment is the responsibility of the Investigator (or medically qualified designee). In determining whether an AE is related to a study procedure, an adverse reaction, Investigators must consider if there is a reasonable possibility of establishing a causal relationship between the event and the study intervention or procedure, based on their analysis of all the available evidence. The assessment must be made on the basis of anticipated effects of these interventions or procedures, as specified in the protocol, or related to the participant's disease, either the disease under investigation or a concurrent illness. The investigator must, whenever possible, provide a causality assessment for AEs based on the information available at reporting and their knowledge of the disease and the effects of the study procedure(s). The Chief Investigator (CI) shall not downgrade the causality assessment provided by an Investigator. Although Investigators must record all AEs in the participant/patient notes they are only required to record AEs on the eCRF for events that are a result of a protocol related procedure.

### 14.2.4 Reporting of a Serious Adverse Event

Investigators are only required to report Serious Adverse Events (SAEs) if they are the result of a protocol procedure as outlined in section 8, meet the regulatory definition of serious (see Section 13.1) and are not listed as expected (see list of expected events below in Section 13.3). Investigators must report all SAEs to the Pharmacovigilance Office, CRUK CTU immediately and under no circumstances should this exceed 24 hours following first awareness of the event by the Investigator or site staff. SAEs must be reported by submitting the SAE eForm on the MACRO database. A paper back up form will be made available and can be used if MACRO access is unavailable. Any SAEs reported on paper must be added to MACRO as soon as possible. The purpose of this obligation is to ensure the CI on behalf of the Sponsor, has the necessary information to continuously assess the benefit-risk balance of the clinical study. For guidance on submitting and completing the initial and follow up SAEs, please refer to the SAE Completion Guidelines, which will be provided by the Pharmacovigilance Office, CRUK Glasgow CTU. The CI will receive notification of all SAEs received. SAEs must be reported locally by the PI at each site in accordance with the local practice at their site (i.e. R&D Office). A follow-up report must be submitted when the SAE resolves, is unlikely to change, or when additional information becomes available. If the SAE meets the criteria for expedited reporting to the REC, then follow up information must be provided as quickly as possible and, in the timeframe, requested by the CRUK CTU and CI. All follow-up information is required to be reported promptly and follow up reports must be submitted until all AEs listed on the initial SAE report resolve or will never resolve. A follow up report should also be submitted if additional AEs occur, or new information becomes available about previously reported AEs. SAEs are required to be reported from Visit 1 for up to 180 days after the last study procedure in that participant.

Any event that meets the criteria of a SAE (including events that the Investigator thinks are medically important but maybe do not require hospitalisation or are fatal) that occur after this 180-day interval should also be reported, if the Investigator thinks these are a late consequence of the study procedures. The Investigator must report such events as SAEs to the CRUK Glasgow CTU Pharmacovigilance Office, using the SAE form, without undue delay. Investigators must follow-up serious and related events, whether they are expected by providing follow-up SAE reports until the reaction has completely resolved or will never resolve. Note that further elective hospital admissions or emergency admissions or death due to disease progression or treatment toxicities do not require to be reported as part of the study but must be recorded in the eCRF. For any questions relating to SAE reporting, please contact the Pharmacovigilance team:

**Pharmacovigilance Office, CRUK Glasgow CTU**
**Email:** mvls-ctu-pv@glasgow.ac.uk
**Telephone**: 0141 211 3567/0203/3968 or 232 2068

Contact details are also provided at the front of the protocol and in the SAE completion guidelines.

## 14.3 EXPECTED EVENTS

The following list of events are expected as a result of the study procedures.

### 14.3.1 Venous Blood Sampling

Venous blood sampling is not expected to present any additional risk to participants.

### 14.3.2 Exhaled Breath Tests

Exhaled breath tests are not expected to present any additional risk to participants.

### 14.3.3 Chest Radiograph

Chest radiographs are not expected to present any additional risk to participants.

### 14.3.4 Magnetic Resonance Imaging (MRI)

**Common** (1/10 to 1/100)

1. Headache
2. Nausea

**Uncommon** (1/100 to 1/1000)

1. Injection site sensations including coldness and warmth
2. Dizziness
3. Dyspnoea
4. Dysgeusia, paraesthesia or itch
5. Vomiting

**Rare** (<1/1000)

1. Anaphylaxis/anaphylactoid reactions
2. Nephrogenic systemic fibrosis

### 14.3.5 Local Anaesthetic Thoracoscopy (LAT)

**Common** (1/10 to 1/100)

1. Pain
2. Post-procedural pneumonia
3. Subcutaneous emphysema
4. Minor haemorrhage (port site or biopsy site) not requiring any intervention or transfusion

**Uncommon** (1/100 to 1/1000)

1. Port site infection requiring antibiotics or pleural empyema
2. Hypotension during procedure requiring additional fluids and/or vasopressors
3. Atrial fibrillation
4. Haemorrhage (port site or biopsy site) requiring intervention during procedure and/or transfusion
5. Port site tumour growth during subsequent follow-up period
6. Post-procedural pneumothorax with an air leak that delays tube removal or prolongs admission
7. Failure of procedure

### 14.3.6 Video-assisted Thoracoscopic Surgery (VATS)

**Common** (1/10 to 1/100)

1. Pain
2. Post-procedural pneumonia
3. Subcutaneous emphysema
4. Minor haemorrhage (port site or biopsy site) not requiring any intervention or transfusion

**Uncommon** (1/100 to 1/1000)

1. Port site infection requiring antibiotics or pleural empyema
2. Hypotension during procedure requiring additional fluids and/or vasopressors
3. Cardiac arrhythmia, including atrial fibrillation
4. Air embolism

5. Haemorrhage (port site or biopsy site) requiring intervention during procedure and/or transfusion
6. Port site tumour growth during subsequent follow-up period
7. Post-procedural pneumothorax with an air leak that delays tube removal or prolongs admission
8. Failure of procedure
9. Complications of general anaesthesia, e.g., anaphylaxis or idiosyncratic reaction to anaesthetic drugs
10. Complications of intubation, including throat pain, mucosal ulceration, laryngeal injury, including hoarseness, tracheal injury

#### 14.3.7 Image-guided Pleural Biopsy

**Common** (1/10 to 1/100)

1. Pain
2. Dyspnoea
3. Minor haemorrhage not requiring any intervention or transfusion
4. Pneumothorax not requiring any intervention

**Uncommon** (1/100 to 1/1000)

1. Haemorrhage requiring intervention during procedure and/or transfusion
2. Pneumothorax requiring intercostal drain insertion and/or hospital admission
3. Biopsy site tumour growth during subsequent follow-up period
4. Failure of procedure

### 14.4 IDENTIFYING EVENTS FOR EXPEDITED REPORTING

The assessment of SAEs for expedited reporting will be undertaken by the CTU and CI based on the list of expected events recorded in the study protocol at the time the SAE report is received. When deciding if an event is unexpected consideration will be made by the CI as to whether the event adds significant information on the specificity, increase of occurrence or severity of a known, serious, and related event that is already recognised and documented in the protocol.

### 14.5 EXPEDITED REPORTS

CRUK CTU on behalf of the Sponsor is responsible for the expedited reporting of all serious, related, and unexpected events to the REC, Sponsor and PIs and study sites. The CI (or CI designee) is responsible for deciding if an event is unexpected and requires expedited reporting. The requirement for expedited reporting starts with the first Research Ethics Committee (REC) approval of the study. It ends with the completion of the study for all participants recruited). SAEs will be reported to the REC where in the opinion of the CI the event was **both**:

- Related – that is, it resulted from administration of any of the research procedures
- Unexpected– that is, the type of event is not listed in the protocol as an expected event

Reports of related and unexpected SAEs will be generated from the study database and signed by the CI. The report will then be submitted within 15 days of the CRUK Glasgow CTU becoming aware of the event, using the 'Report of Serious Adverse Event form' for non-CTIMPs (Clinical Trial of an Investigational Medicinal Product) published by the HRA. If the assessment of causality provided by the investigator differs from that of the CI (assessment is made on behalf of the sponsor), the opinion of both the investigator and CI will be provided in the expedited report. Investigators will receive all expedited reports. The CI will assess if the risk-benefit assessment has been affected by each serious, related and unexpected event they identify. If the risk-benefit of participation is adversely affected, appropriate prompt action will be decided upon by the CI, Sponsor and Study Steering Committee (SSC) and implemented by the Study Management Group (SMG).

### 14.6 PREGNANCY REPORTING

Pregnancy occurring in a clinical trial participant, while not considered an AE or a SAE, requires monitoring and follow-up. The Investigator must collect pregnancy information for female trial subjects in Arm A only during the 2 years on study. The Investigator must ensure that all patients on Arm A are aware at the start of a clinical trial of the importance of reporting all pregnancies that occur during the 2 years on study. The Investigator should offer counselling to the patient and discuss the risks of continuing with the pregnancy and the possible side effects on the foetus. Monitoring of the patient and the baby should continue until the conclusion of the pregnancy if the patient has given approval for this. If a patient does become pregnant this must be reported to the Pharmacovigilance Department within 24 hours of the site staff becoming aware of it. Initially this should be reported by completing the pregnancy notification eForm, followed up immediately by completing and submitting a Pregnancy Notification Form (PNF) by email to: mvls-ctu-pv@glasgow.ac.uk

It is the Investigator's responsibility to obtain approval from the patient for following up the pregnancy until outcome. The Pharmacovigilance Department of the CRUK Glasgow CTU will follow-up all pregnancies until the pregnancy outcome via the Investigator, using the PNF. The Investigator must update the PNF with the outcome of the delivery or if there is a change in the subject's condition, such as miscarriage or planned termination, or new relevant information becomes available concerning the child. The updated PNF must be submitted to the Pharmacovigilance Department as soon as the information becomes available and no later than within 24 hours of first becoming aware of the change in condition or new information.

Any pregnancies which result in a congenital anomaly or birth defect will require to be reported by the Investigator as a SAE. The Pharmacovigilance Department will assist with providing guidance on reporting pregnancy outcomes as SAEs. SAEs that are the result of a birth defect will be reported as serious, related and unexpected events.

### 14.7 STUDY INTERVENTION ERRORS

Intervention errors require monitoring and follow-up. Report all errors as SAEs.

### 14.8 ANNUAL PROGRESS REPORT

An annual progress report including information on the safety of study participants if relevant, will be prepared by the PM and submitted to the REC.

### 14.9 MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA) REPORTING

There is no statutory requirement to report SAEs to the MHRA for clinical research which does not fall under the requirements of the Medicines for Human Use (Clinical Trials) Regulations such as non-CTIMPs.

## 15 STATISTICS AND DATA ANALYSIS

### 15.1 SAMPLE SIZE AND ASSUMPTIONS

The sample size estimate for Arm A is 500, based on the outcome of the retrospective arm of Meso-ORIGINS feasibility study[20] and using prediction intervals (PI) for binomial data, as proposed by Lu & Jin[40]. In this retrospective multi-centre cohort study, MPM evolved following an initial diagnosis of asbestos associated benign pleural inflammation in 42 of 257 eligible cases (16%, 95%CI: (12.3, 21.4%)). Of these, MPM evolution was confirmed histologically by repeat biopsy in 36/257 (14%, 95% CI: (10.3, 18.8)). Recruitment of 500 cases to Meso-ORIGINS will therefore generate 63 (95% PI: (41, 89)) biopsy-confirmed MPM evolutions, assuming 10% loss to follow-up (i.e., 450 cases completing follow-up). 500 recruits will also generate 387 (95% PI (361, 409)) participants in whom MPM will not evolve within 2 years. Based on the prospective arm of the Meso-ORIGINS

feasibility study, repeat benign biopsies (by either LAT or image-guided biopsy) 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. If all cases are re-biopsied by LAT, 148 (95% PI: (90, 213)) cases will be available. If all are re-biopsied by image guided, 180 (95% PI: (114, 248)) cases will be available. The MRI sub-study will recruit at least 100, including an estimated 13 cases in whom MPM will evolve. Assuming 10% loss to follow up (i.e. 90 cases with complete follow-up) and the evolution rate in the sub-study tracks the rate in Arm A overall (14%, 95% CI: (10.3, 18.8)

The sample size estimate for Arm B is 250, which is expected to generate at least 91 MPM cases (one-sided 95% PI: (91, +ve Inf)) based on a previous study by our group, in which 69/155 (44.5%) participants with asbestos exposure and a clinical suspicion of MPM had MPM confirmed at LAT.[22] The size of the arm has been increased from an original arbitrary estimate of 39, and subsequent increase to 120. These changes follow publication of a recent study by Zhang et al which reported highly complex exomic intra-tumour heterogeneity (ITH) based on 90 multi-region pleural biopsies collected from 22 MPM patients[4], and increased requirements for the tissue and data being generated from downstream laboratory partners. A review of recruitment in December 2023 revealed 94 Arm B recruits, recruited over 19 months, with a crude average of 5 cases/month. However, recruitment rate has been steadily increasing, and varied between 7 and 11 cases/month over 6 recent months. Supported by the imminent opening of 7 additional sites, bringing the total number of sites to 25, we conservatively predict an average recruitment of 9 cases/month over the remaining 19 months. This translates into 265 available cases by study end and exceeds the updated sample size estimate of 250. The larger number of confirmed MPM cases (n=91) predicted from this cohort will generate an estimated 364 multi-region MPM biopsies (assuming 4 biopsies/case), increasing the pool of samples for ITH assessment by x7.6fold. This interim recruitment review also demonstrated the feasibility of transitioning Arm B cases with benign pleural biopsies (40/94 (43%) recruits) to Arm A, with 23/35 (66%) such cases approached entering Arm A after completing Arm B. This practice will generate an estimated 76 additional Arm A recruits via Arm B transition, of whom 11 are expected to evolve to MPM (based on 14% (95% CI 10.5-19.2)). This will facilitate linkage of pre-MPM multi-region biopsies with subsequent MPM evolution and non-evolution status, which will greatly enhance target ID and rationalisation opportunities for development of chemoprophylaxis (pre-MPM) therapies.

## 15.2 ANALYSIS PLAN

### 15.2.1 Primary Endpoint Analysis

The primary endpoint will be reported by simple descriptive statistics. The confidence interval will be based on the Agresti-Coull approach[41].

### 15.2.2 Secondary Endpoint Analyses

- A classification model for MPM evolution will be generated using the XGBoost tree boosting system[42], where SHAP values will be used to evaluate the contribution of each feature to individual predictions[43]. The performance of the developed model will be assessed using a Receiver Operator Characteristic curve. Any model developed will be subject to subsequent validation in and independent data set.
- The number of participants in Arm B with confirmed MPM following thoracoscopy will be reported by simple descriptive statistics. The confidence interval will be based on the Agresti-Coull approach[41].
- The downstream heterogeneity analyses will be performed by Prof Crispin Miller (Head of Bioinformatics, Beatson Institute of Cancer Research, Glasgow) and reported separately.

### 15.2.3 Safety Analysis

Adverse event data will be summarised in tables and listings.

### 15.2.4 Interim Analyses

There are no planned interim analyses, however the primary endpoint will be performed regularly during the study and reported at SMG Meetings to ensure sufficient tissue pairs are being collected.

# 16 STUDY CLOSURE/DEFINITION OF END OF THE STUDY

The study will end on the date of last data capture.

## 16.1 END OF STUDY NOTIFICATION/DECLARATION OF THE END OF A STUDY FORM

An end of study notification will be submitted to the ethics committee within 90 days using the 'Declaration of the end of a study' form. However, if the study is terminated either (1) before the date specified in the protocol or (2) before the required number of events has occurred, the ethics committee will be notified in writing within 15 days of termination with an explanation and details of follow-up measures, if any, taken for safety reasons.

## 16.2 CLINICAL STUDY SUMMARY REPORT

The CI in association with both PREDICT-Meso PM and CRUK Glasgow CTU, is responsible for compiling and submitting the final report to both Sponsor and the REC.

## 16.3 TEMPORARY HALT OF THE STUDY

If recruitment needs to be temporarily halted for reasons not specified in the protocol, the Sponsor will inform the REC immediately and at the latest within 15 days. This includes studies where the stoppage was not envisaged in the approved protocol and where there is an intention to resume. It does not include studies where recruitment may be temporarily halted for logistical reasons such as study team availability. The notification will be made as a substantial amendment and will clearly state what activities have been halted and the reasons for this. To restart a study that has been temporarily halted the Sponsor will make a request as a substantial amendment providing evidence that it is safe to restart. If the Sponsor decides not to recommence the study, the REC will be notified in writing within 15 days of the decision, using the end-of-study declaration form.

## 16.4 EARLY TERMINATION OF A STUDY

In the case of early termination, the Sponsor will notify the REC immediately and at the latest within 15 days, explaining the reasons and describing the follow-up measures, if any, to be taken for safety reasons. This does not include studies that complete early because full recruitment has been achieved.

# 17 DATA HANDLING

## 17.1 ELECTRONIC CASE REPORT FORMS (ECRFS)

The CRFs for this study will be completed using the electronic remote data capture (eRDC) system, MACRO®. Prior to recruitment beginning at each site, the MACRO® User Guide will be sent to sites. It is the responsibility of the PI to ensure eCRFs are completed in a timely manner (within 4-6 weeks of the study visit) and to review and approve all data captured on the eCRF. **Please ensure that all data submitted on eCRFs are verifiable in the source documentation or that any discrepancies are recorded and explained.** In addition to completing the MACRO® database there will be paper CRFs, including registration forms, which should be completed prior to calling or emailing CRUK CTU. The pregnancy notification form will also continue to be a paper form and a paper version of the SAE form will be provided for use when MACRO access is unavailable. Please refer to the **Data**

**Completion Guideline** document in the Investigator site file (ISF). Please also note that some study forms must be signed by the PI or another clinician delegated to do so on the delegation log. These forms will be defined in the completion guidelines. Other essential documents, including source data, consent forms, and regulatory documentation, will be archived by, or for the Investigator, in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection as required.

### 17.2 CENTRAL REVIEW OF DATA

CRUK Glasgow CTU will regularly review the data for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found within the eCRFs upon CTU review, queries will be generated within the MACRO® study database for the site to access and resolve. Sites are expected to review and respond to queries within the database in a timely manner (within 4-6 weeks). Any issues identified at sites related to poor data/slow response to queries will be managed as per the data escalation process below.

### 17.3 DATA ESCALATION PROCESSES

Where issues with data return/quality/response to requests are identified at sites, the following process will be followed:

- Step 1: E-mail letter to site main contact and copy in site PI
- Step 2: E-mail letter direct to site PI and copy in site main contact
- Step 3 E-mail letter to NIHR Network Coordinator and copy in site PI and main contact
- Step 4: Discuss suspension of recruitment at site until data issues resolved

### 17.4 RECORD RETENTION AND ARCHIVING

Archiving of the study essential documents should be performed by both the participating study site and Sponsor/ PREDICT-Meso PM/CRUK Glasgow CTU.

Participating sites are responsible for archiving their study related documentation and should follow the requirements of their R&D Office in conjunction with advice from the Project Manager and Sponsor regarding the duration of document retention. Sites should not archive their study documentation until they have been instructed by the Project Manager or Sponsor that they are able to do so. Where possible, at the time of archiving, sites will be notified of the archiving retention period. If this is not confirmed at the time of archiving, sites should not destroy archived documentation until authorisation is given from the Sponsor. The Sponsor and Project Manager will be responsible for archiving the Trial Master File (TMF) and all other essential study documentation that is not held at participating study sites as per their applicable Standard Operating Procedures (SOPs).

If a participant's care is transferred to another hospital a Patient Transfer Form must be completed by the original recruiting site (or the current site responsible for the patient/participant) to request that the transfer is performed within the CTU and MACRO® system. The original recruiting site will be recognised with the recruitment of the participant. The original (or current) site will be responsible for ensuring all is up to date prior to the transfer of the participant on the MACRO® system. Once the transfer has been processed, the new site will be responsible for returning all outstanding study documents from that point onwards including any outstanding data prior to the date of transfer.

# 18 STUDY MANAGEMENT

## 18.1 STUDY START UP

Sites wishing to participate in the study should contact the PREDICT-Meso PM (Contact details are provided at the front of the protocol). A PI must lead the study at each site, and they will be responsible for providing all core documentation. Protocol training will be given to sites via initiation slides that will be provided to sites prior to the study opening at that site. Once all documentation is received, an initiation call will be performed. Sites will receive an email from the CTU to confirm they are activated and are able to recruit participants to the study.

## 18.2 CORE DOCUMENTS

- Local R&D approval / Confirmation of capacity and capability
- Signed Clinical Study Agreement
- Delegation and training logs completed by all members of the study team and signed off by the PI
- CV and Good Clinical Practice (GCP) certificates for the PI
- PIS, GP letter and participant results letter on local headed paper
- Completed site capability form
- Initiation acknowledgements from all members of the study team confirmation the protocol and initiation slides have been reviewed
- Normal ranges and accreditation certificates for biochemistry and haematology departments

## 18.3 MANAGEMENT OF PROTOCOL DEVIATIONS AND VIOLATIONS

### 18.3.1 Deviations

Organisations must notify the Sponsor, via PREDICT-Meso PM, of all deviations from the protocol or GCP immediately. The Sponsor requires a report on the incident(s) and a deviation form will be provided to site for completion. This should be completed by site as soon as possible and returned to the PREDICT-Meso PM. Omitted clinical tests at baseline or follow-up (e.g., CT scans) or missed research samples of blood, breath and pleural fluid do not constitute protocol violations. In contrast, failed retrieval of FFPE pleural biopsies should be treated as a protocol violation. If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the PREDICT-Meso PM/CRUK Glasgow CTU study team and Sponsor can be contacted immediately to discuss. The Sponsor will assess all incidents with respect to the criteria of a “serious breach”.

### 18.3.2 Serious Breach

Events that match the criteria of a “serious breach” will be reported to the REC within 7 days of the matter coming to the attention of the Sponsor. National Research Ethics Service SOP for Research Ethics Committees (version 6.1, January 2015) defines a serious breach as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards of conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of study subjects or the scientific value of the research. The report should include details of when the breach occurred, the location, who was involved, the outcome and any information given to participants. The REC should also be informed of any corrective or preventative actions planned.

## 18.4 STUDY MANAGEMENT GROUP (SMG)

The study will be coordinated by the PREDICT-Meso Network supported by CRUK CTU and the SMG. The SMG includes those individuals responsible for day-to-day management, including the CI, Co-Investigators, CTU-PM, Network PM, Study Statistician, Pharmacovigilance, Clinical Trials Coordinator (CTC) and Participant

Representative. The role of the SMG is to monitor the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the study.

# 19 REGULATORY ISSUES

## 19.1 ETHICS APPROVAL

The study will be conducted in line with the current Government, HRA and health board guidance regarding COVID-19. Favourable ethical opinion will be sought from the West of Scotland REC before any participants are recruited. The CI will be responsible for updating the ethics committee of any new information related to the study. Each participating site will be responsible for obtaining their own local R&D approval prior to opening the study. For sites within England or Wales, HRA approval is also required. Participating sites will not be activated to recruitment until all documents have been returned and necessary approvals are in place. The CRUK Glasgow CTU will send a site opening email to site and activate the site on local system. The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh [2000]).

## 19.2 CONSENT

Consent must be received from each participant after a full explanation of the study, provision of an information sheet, and sufficient time, in the patient's own judgment, to consideration involvement. Same-day consent is permissible in participants who are comfortable with this, since recruitment opportunities may be infrequent, with routine clinic reviews typically occurring every 6 months. However, if participants would like more time to consider involvement, a follow-up telephone call with a member of the study team will be offered. Signed participant consent must be obtained, the consent forms should also be signed by the person carrying out the consent procedure at site, who must be detailed on the study specific delegation and training log as having authorisation. The PI is responsible for ensuring that those designated with receipt of consent are suitably qualified by training or experience. Arm A, the Arm A MRI sub-study and Arm B will all have separate consent forms, which are supported by individual participant information sheets. In addition, participants who decline follow up visits can consent to remote observation which has a separate consent form. Remote consent can be received from participants opting for remote observation, who may not be physically on-site with study staff and will not attend further clinics to allow deferred signing. In such cases, the study should be introduced and discussed by phone initially. The PIS and consent form should then be sent to the potential participant in the post or by email. A follow-up phone call should then be arranged for further discussion. During this call the participant can sign the consent form remotely and return this by post or email, for PI or designated team member to complete the form. The researcher must record the following dates in the patient notes: initial telephone call/ agreement to send the PIS to the patient; follow up telephone call / agreed remote consent; date form received and fully signed. The right of the participant to refuse to participate without giving reasons must be respected, and this will be made clear to all those approached. All participants are free to withdraw at any time, without giving reasons and without prejudicing further treatment (see section 6.6 for detail). An original completed consent form must be retained at each site in the appropriate section of the Investigator Site File, and a photocopy placed in the participant's medical records. All participants must be given either an original or a copy (as per local site practice) of the signed participant information sheet and consent form for their records. Consent forms must be retained on site and not submitted to the CRUK Glasgow CTU. If new participant information sheets/consent forms are produced during the study, participants already participating in the study may need to be re-consented to the updated participant information sheet. However, if the site PI decides this

is not in the best interests of the participant, re-consent is not required. Decisions not to re-consent participants must be documented in the participant's medical records.

### 19.3 CONFIDENTIALITY

All information collected during the course of the study will be kept strictly confidential. Information will be held securely on paper and electronically at the CRUK Glasgow CTU. The CRUK Glasgow CTU will comply with all aspects of the 2018 Data Protection Act and operationally this will include:

- Consent to record personal details including initials, date of birth, GP name and address.
- Appropriate storage, restricted access and disposal arrangements for personal and clinical details
- Consent for access to participant's medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to study participation
- Consent for the data collected in the study to be used to evaluate safety and develop new research.
- Where central monitoring of source documents by CRUK Glasgow CTU (or copies of these) are required (e.g., scans, blood results), the participant's name must be obliterated by site before sending.
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CRUK Glasgow CTU.
- If a participant withdraws consent from further study procedures and/or further collection of data their samples will remain on file and will be included in the final analysis unless they specifically withdraw consent for this.

### 19.4 LIABILITY, INDEMNITY AND INSURANCE

No special insurance is in place for participants in this study other than standard NHS liability insurance providing indemnity against clinical negligence. This does not provide cover for non-negligence e.g., harm caused by an unexpected side effect of participating in a study. The sponsors have responsibility for ensuring that financial cover for damages or compensation arising from no fault harm is available to participants, where applicable. The University of Glasgow maintains clinical trials insurance. Cover for this study has been agreed under the current policy. The Hospital Trust/Health Board at each participating site is responsible for the following:

1. Acts and omissions of its own staff and others engaged by it, including the Clinical Trials Unit and PI
2. Ensuring the appropriate insurance administered by the NHS Litigation Authority is in place
3. Ensuring any non-NHS employees involved in the clinical study have Honorary Contracts with the Trust/Board to cover access to participants and liability arrangements

These responsibilities are outlined and agreed within the Clinical Study Agreement.

### 19.5 SPONSOR

NHS Greater Glasgow and Clyde will act as the main sponsor for this study. Delegated activities will be assigned to the PREDICT-Meso PM/CRUK Glasgow CTU and NHS Trusts/Boards taking part in this study. Details of responsibilities will be outlined in the clinical study agreement that should be signed prior to site initiation.

### 19.6 FUNDING

This study is being funded by a grant from Cancer Research UK for the PREDICT-Meso Accelerator Programme (Grant Reference C57060/A29372). Site payments are available and are documented in the site agreement.

## 19.7 PROTOCOL AMENDMENTS

Any change to the study protocol will require an amendment. Any proposed, non-administrative, protocol amendments will be initiated by the CI following discussion with the SMG and any required amendment forms will be submitted to the regulatory authority, ethics committee and sponsor(s). The CI and the SMG will liaise with sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and sponsor representative. Before the amended protocol can be implemented favourable approval must be sought from the original reviewing REC, study Sponsor, HRA (English/Welsh sites only) and participating site R&D offices.

## 19.8 ALLOCATION OF STUDY RESPONSIBILITIES

### 19.8.1 Sponsor Responsibilities (NHS GG&C)

The Sponsor is responsible for confirming there are proper arrangements for the initiation and management of the study. Any Sponsor's responsibilities that have been delegated to the CI will be documented within the 'Responsibilities delegated to the Chief Investigator' form. The duties will be performed via the PREDICT-Meso PM as the co-ordinator for the study.

### 19.8.2 Chief Investigator (CI)

The CI is directly responsible for:

- Ensuring the protocol and any amendments are in place.
- Clinical oversight of the safety of participants participating in the study, including the ongoing review of the risk/benefit.
- For review of SAEs and determination if SAEs meet the criteria for expedited reporting within 24 hours.
- Providing advice and recommendations on medical issues that arise involving the management of the participants on the study.

### 19.8.3 PREDICT-Meso Network

The PREDICT-Meso PM delivers the overall management of the study. This includes, but is not limited to, all regulatory submissions (ethics, HRA, and R&D) and any amendments, all administration relating to the submissions and any amendments, circulation of all correspondence to participating sites, ongoing communication with participating sites, and where applicable the management of any financial arrangements.

### 19.8.4 CRUK Clinical Trials Unit (CTU)

The CRUK CTU will deliver data management, central monitoring of data quality and safety, and management of safety reporting.

### 19.8.5 Participating Site

The Participating Site is solely responsible for the management of the study within their site. This includes ensuring local management approval has been given, ensuring the study is conducted according to GCP requirements, and ensuring the appropriate insurance or indemnity is in place. The Participating Site is also responsible for arranging access for on-site monitoring and auditing as identified in the study protocol and also for regulatory inspections.

### 19.8.6 Principal Investigator (PI)

The PI is responsible for:

- The delegation of study activities within their site and ensuring all personnel are adequately trained and qualified to carry out their responsibilities
- Providing evidence of GCP training (usually a certificate) or undergo the required GCP training
- The safety and wellbeing of study participants
- Reporting any deviations from the protocol to PREDICT-Meso PM
- Reporting any SAEs or safety issues within 24 hours of becoming aware, including assignation of seriousness and causality Full details of the responsibilities of the PI are outlined in the Clinical Study Agreement. Two original copies of this will be held – one with the Sponsor and the other at the participating site. A photocopy of the signed agreement will also be held at the coordinating trial office.

# 20 QUALITY ASSURANCE

## 20.1 AUDITS AND INSPECTIONS

Study Investigators must permit study related monitoring, audits, REC review and regulatory inspections as required, by providing direct access to source data, eCRFs and other documents (participant medical records, investigator site file, and other pertinent data). The study may be subject to inspection and audit by NHS Greater Glasgow and Clyde as Sponsor, or the CRUK Glasgow CTU, to ensure adherence to GCP. If an inspection is scheduled at any participating site, the site must notify the Sponsor at the earliest opportunity. It is the sponsor's responsibility to inform the investigator(s) of all intended audits and regulatory inspections involving the participating site. It is the investigator's responsibility to ensure appropriate resources at site and that the inspector(s) have access to all source data.

## 20.2 ON SITE AND TELEPHONE MONITORING

Since the study is not a CTIMP, there will be no onsite or telephone monitoring.

## 20.3 PROTOCOL NON-COMPLIANCE

Protocol non-compliances (see Section 17.3.1) must be reported by the site study team to the PREDICT-Meso PM as soon as they are identified. Non-compliances may also be identified by the PREDICT-Meso PM, CTU-PM/CTC. Where identified, site staff and the PREDICT-Meso PM will work together to complete a protocol deviation form and put corrective and preventive actions in place. Where the deviation is of a more serious nature, the Sponsor may be required to report a serious breach of protocol to the Ethics Committee. The Sponsor reserves the right to suspend recruitment at a site until an investigation has taken place and corrective and preventive measures have been put in place to ensure future participant safety and/or data integrity.

# 21 PUBLICATION POLICY

The Meso-ORIGINS SMG is responsible for approving the content and dissemination of all publications, abstracts and presentations arising from the study and for assuring the confidentiality and integrity of the study. The International Committee of Medical Journal Editors (ICMJE) criteria http://www.icmje.org/icmje-recommendations.pdf) will be used to ensure all those contributing are appropriately acknowledged. No site or individual will publish data without prior approval of the SMG.

# 22 DATA OWNERSHIP

The data arising from Meso-ORIGINS will belong to the study Sponsor, NHS Greater Glasgow and Clyde. The PREDICT-Meso Network (under the care of University of Glasgow) is a joint controller of data, images and samples collected in this study. Samples and data collected from the Meso-ORIGINS study will be stored in the PREDICT-Meso Research Tissue Bank (RTB) (REC reference 21/WS/0011). The PREDICT-Meso Network and RTB

shall act as custodian of these samples, images and data, and shall make these available to PREDICT-Meso Network partners upon successful application review, in line with PREDICT-Meso RTB policy. Further information on the PREDICT-Meso RTB is available via the PREDICT-Meso PM.

# 23 REFERENCES

1. Beckett P, Edwards J, Fennell D, Hubbard R, Woolhouse I, Peake MD. Demographics, management and survival of patients with malignant pleural mesothelioma in the National Lung Cancer Audit in England and Wales. *Lung Cancer*. 2015;88(3):344-348. doi:10.1016/j.lungcan.2015.03.005

2. Kidd AC, McGettrick M, Tsim S, Halligan DL, Bylesjo M, Blyth KG. Survival prediction in mesothelioma using a scalable Lasso regression model: instructions for use and initial performance using clinical predictors. *BMJ Open Respiratory Research*. 2018;5(1):e000240. doi:10.1136/bmjresp-2017-000240

3. Hmeljak J, Sanchez-Vega F, Hoadley KA, et al. Integrative Molecular Characterization of Malignant Pleural Mesothelioma. *Cancer discovery*. 2018;8(12):1548-1565. doi:10.1158/2159-8290.cd-18-0804

4. Zhang M, Luo J-L, Sun Q, et al. Clonal architecture in mesothelioma is prognostic and shapes the tumour microenvironment. *Nat Commun*. 2021;12(1):1751. doi:10.1038/s41467-021-21798-w

5. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *Lancet*. Published online 2021. doi:10.1016/s0140-6736(20)32714-8

6. National Lung Cancer Audit pleural mesothelioma report 2016 (for the audit period 2014). Published online December 11, 2016:1-38.

7. Delgermaa V, Takahashi K, Park E-K, Le GV, Hara T, Sorahan T. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. *Bulletin of the World Health Organization*. 2011;89(10):716-24-724A-724C. doi:10.2471/blt.11.086678

8. Driscoll T, Nelson DI, Steenland K, et al. The global burden of disease due to occupational carcinogens. *American journal of industrial medicine*. 2005;48(6):419-431. doi:10.1002/ajim.20209

9. Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nature genetics*. 2016;48(4):407-416. doi:10.1038/ng.3520

10. Chernova T, Murphy FA, Galavotti S, et al. Long-Fiber Carbon Nanotubes Replicate Asbestos-Induced Mesothelioma with Disruption of the Tumor Suppressor Gene Cdkn2a (Ink4a/Arf). *Current biology : CB*. 2017;27(21):3302-3314.e6. doi:10.1016/j.cub.2017.09.007

11. Davies HE, Nicholson JE, Rahman NM, Wilkinson EM, Davies RJO, Lee YCG. Outcome of patients with nonspecific pleuritis/fibrosis on thoracoscopic pleural biopsies. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2010;38(4):472-477. doi:10.1016/j.ejcts.2010.01.057

12. Yang Y, Wu Y-B, Wang Z, et al. Long-term outcome of patients with nonspecific pleurisy at medical thoracoscopy. *Resp Med*. 2017;124:1-5. doi:10.1016/j.rmed.2017.01.005

13. Metintas M, Ak G, Cadirci O, Yildirim H, Dundar E, Metintas S. Outcome of patients diagnosed with fibrinous pleuritis after medical thoracoscopy. *Resp Med*. 2012;106(8):1177-1183. doi:10.1016/j.rmed.2012.04.009

14. Reuter SB, Clementsen PF, Bodtger U. Incidence of malignancy and survival in patients with idiopathic pleuritis. *J Thorac Dis*. 2019;11(2):386-392. doi:10.21037/jtd.2018.12.136

15. Eisenstadt HB. Benign Asbestos Pleurisy. *Jama*. 1965;192(5):419-421. doi:10.1001/jama.1965.03080180077029

16. Hegmans JPJJ, Hemmes A, Hammad H, Boon L, Hoogsteden HC, Lambrecht BN. Mesothelioma environment comprises cytokines and T-regulatory cells that suppress immune responses. *Eur Respir J*. 2006;27(6):1086-1095. doi:10.1183/09031936.06.00135305

17. Wu C, Mairinger F, Casanova R, Batavia AA, Leblond A-L, Soltermann A. Prognostic Immune Cell Profiling of Malignant Pleural Effusion Patients by Computerized Immunohistochemical and Transcriptional Analysis. *Cancers*. 2019;11(12):1953. doi:10.3390/cancers11121953

18. Comertpay S, Pastorino S, Tanji M, et al. Evaluation of clonal origin of malignant mesothelioma. *Journal of translational medicine*. 2014;12(1):301. doi:10.1186/s12967-014-0301-3

19. Kiyotani K, Park J-H, Inoue H, et al. Integrated analysis of somatic mutations and immune microenvironment in malignant pleural mesothelioma. *Oncoimmunology*. 2017;6(2):e1278330. doi:10.1080/2162402x.2016.1278330

20. Ferguson K, Mercer R, King J, et al. S43 Preliminary results of the Meso-ORIGINS feasibility study: retrospective element regarding BAPE-mesothelioma evolution rate. *Thorax*. 2021;76(Suppl 1):A28-A28. doi:10.1136/thorax-2020-btsabstracts.48

21. Hjerpe A, Ascoli V, Bedrossian CWM, et al. Guidelines for the cytopathologic diagnosis of epithelioid and mixed-type malignant mesothelioma: Complementary Statement from the International Mesothelioma Interest Group, Also Endorsed by the International Academy of Cytology and the Papanicolaou Society of Cytopathology. Michael CW, ed. Published online July 2015.

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

23. Woolhouse I, Bishop L, Darlison L, et al. British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. *Thorax*. 2018;73(Suppl 1):i1-i30. doi:10.1136/thoraxjnl-2017-211321

24. Scherpereel A, Opitz I, Berghmans T, et al. ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma. *Eur Respir J*. 2020;55(6):1900953. doi:10.1183/13993003.00953-2019

25. Hooper C, Lee YCG, Maskell N, Group BPG. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. Published online August 2010.

26. Zocchi L. Physiology and pathophysiology of pleural fluid turnover. *Eur Respir J*. 2002;20(6):1545-1558. doi:10.1183/09031936.02.00062102

27. Donaldson K, Brown GM, Brown DM, Bolton RE, Davis JM. Inflammation generating potential of long and short fibre amosite asbestos samples. *British journal of industrial medicine*. 1989;46(4):271-276.

28. Hodgson JT, McElvenny DM, Darnton AJ, Price MJ, Peto J. The expected burden of mesothelioma mortality in Great Britain from 2002 to 2050. *Br J Cancer*. 2005;92(3):587-593. doi:10.1038/sj.bjc.6602307

29. Seely JM, Nguyen ET, Churg AM, Müller NL. Malignant pleural mesothelioma: computed tomography and correlation with histology. *Eur J Radiol*. 2009;70(3):485-491. doi:10.1016/j.ejrad.2008.02.004

30. Metintas M, Ucgun I, Elbek O, et al. Computed tomography features in malignant pleural mesothelioma and other commonly seen pleural diseases. *Eur J Radiol*. 2002;41(1):1-9.

31. Tsim S, Stobo DB, Alexander L, Kelly C, Blyth KG. The diagnostic performance of routinely acquired and reported computed tomography imaging in patients presenting with suspected pleural malignancy. *Lung Cancer*. 2017;103:38-43. doi:10.1016/j.lungcan.2016.11.010

32. Tsim S, Humphreys CA, Cowell GW, et al. Early Contrast Enhancement: A novel magnetic resonance imaging biomarker of pleural malignancy. *Lung Cancer*. 2018;118:48-56. doi:10.1016/j.lungcan.2018.01.014

33. Marchetti G, Valsecchi A, Indellicati D, Arondi S, Trigiani M, Pinelli V. Ultrasound-guided medical thoracoscopy in the absence of pleural effusion. *Chest*. 2015;147(4):1008-1012. doi:10.1378/chest.14-0637

34. Hallifax RJ, Corcoran JP, Ahmed A, et al. Physician-based ultrasound-guided biopsy for diagnosing pleural disease. *Chest*. 2014;146(4):1001-1006. doi:10.1378/chest.14-0299

35. Lamote K, Brinkman P, Vandermeersch L, et al. Breath analysis by gas chromatography-mass spectrometry and electronic nose to screen for pleural mesothelioma: a cross-sectional case-control study. *Oncotarget*. 2017;8(53):91593-91602. doi:10.18632/oncotarget.21335

36. Lamote K, Vynck M, Cleemput JV, Thas O, Nackaerts K, Meerbeeck JP van. Detection of malignant pleural mesothelioma in exhaled breath by multicapillary column/ion mobility spectrometry (MCC/IMS). *Journal of breath research*. 2016;10(4):046001. doi:10.1088/1752-7155/10/4/046001

37. Lamote K, Vynck M, Thas O, Cleemput JV, Nackaerts K, Meerbeeck JP van. Exhaled breath to screen for malignant pleural mesothelioma: a validation study. *Eur Respir J*. 2017;50(6):1700919. doi:10.1183/13993003.00919-2017

38. Rahman NM, Ali NJ, Brown G, et al. Local anaesthetic thoracoscopy: British Thoracic Society Pleural Disease Guideline 2010. Published online August 2010.

39. Viskum K, Enk B. Complications of thoracoscopy. *Le Poumon Et Le Coeur*. 1981;37(1):25-28.

40. Lu H, Jin H. A new prediction interval for binomial random variable based on inferential models. *J Stat Plan Infer*. 2020;205:156-174. doi:10.1016/j.jspi.2019.07.001

41. Agresti A, Coull BA. Approximate is Better than "Exact" for Interval Estimation of Binomial Proportions. *Am Statistician*. 1998;52(2):119-126. doi:10.1080/00031305.1998.10480550

42. Krishnapuram B, Shah M, Smola A, et al. Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining, KDD '16. *Proc 22nd Acm Sigkdd Int Conf Knowl Discov Data Min*. Published online 2016:785-794. doi:10.1145/2939672.2939785

43. Lundberg SM, Lee S-I. Consistent feature attribution for tree ensembles. *Arxiv*. Published online 2017.