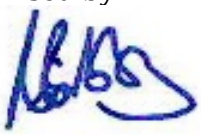
ASSESS-meso

A prospective ob**S**ervational cohort **S**tudy collecting data on d**E**mographics, **S**ymptoms and biomarker**S** in people with **meso**thelioma that will provide a resource for future trials

Chief Investigator: **Dr Anna Bibby**

Protocol Version	1.9
Version date	14/12/2023
IRAS project ID	220360
R&I number	3850a
EudraCT number	61861764

Authorised by:



Dr Anna Bibby
14/12/2023

GENERAL INFORMATION

This document describes the multicentre mesothelioma cohort and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of patients with mesothelioma. Every care was taken in the creation of this document, but corrections or amendments may be necessary.

COMPLIANCE

The trial will be conducted in compliance with the protocol, Research Governance Framework, Data Protection Act and other guidelines as appropriate.

RESEARCH TEAM CONTACTS

Clinical queries should be directed to the local principal investigator, or to the trial co-ordinator or chief investigator

For general queries, supply of trial documentation and collection of data, please contact the trial administrator.

Chief Investigator:

Dr Anna Bibby
Consultant Senior Lecturer
Academic Respiratory Unit
University of Bristol

2nd Floor L&R Building
Southmead Hospital
Bristol
BS10 5NB

Tel: 0117 414 8049
Email: anna.bibby@bristol.ac.uk

Study coordinator:

Mrs Jenny Symonds
Respiratory Research Unit
Clinical Research Centre
Southmead Hospital
Bristol
BS10 5NB

Tel: 0117 414 8114
Jenny.Symonds@nbt.nhs.uk

Sponsor:

North Bristol NHS Trust
Research & Innovation Department
3rd Floor L&R Building
Southmead Hospital
Bristol
BS10 5NB

Tel: 0117 414 9329
Email: Researchsponsor@nbt.nhs.uk

CONTENTS

1. ABBREVIATIONS ..... Page 5
2. STUDY SUMMARY ..... Page 6
    - 2.1 Plain English summary ..... Page 6
    - 2.2 Scientific abstract ..... Page 6
    - 2.3 Study design ..... Page 7
3. BACKGROUND ..... Page 7
    - 3.1 Mesothelioma ..... Page 7
    - 3.2 Biomarkers and predictors of outcome ..... Page 8
    - 3.3 Justification for a mesothelioma cohort ..... Page 8
    - 3.4 The trial within a cohort design ..... Page 9
4. AIMS & OBJECTIVES ..... Page 10
5. METHODOLOGY ..... Page 10
    - 5.1 Setting ..... Page 10
    - 5.2 Inclusion criteria ..... Page 11
    - 5.3 Exclusion criteria ..... Page 11
    - 5.4 Screening, enrolment and consent ..... Page 11
    - 5.5 Consent for future trials within the cohort ..... Page 12
    - 5.6 Sample size & recruitment targets ..... Page 12
    - 5.7 Co-enrolment guidelines ..... Page 13
6. STUDY ASSESSMENTS ..... Page 13
    - 6.1 Baseline assessments ..... Page 13
    - 6.2 Follow up assessments ..... Page 14
    - 6.3 Telephone assessments ..... Page 14
    - 6.4 Study flow diagram ..... Page 14
    - 6.5 Schedule of assessments ..... Page 16
    - 6.6 Questionnaires & patient reported outcomes ..... Page 16
    - 6.7 Biological samples ..... Page 17
    - 6.8 Cessation of follow up ..... Page 18
    - 6.9 Study duration ..... Page 18
    - 6.10 Source data ..... Page 19
7. STATISTICAL ANALYSIS PLAN ..... Page 19
8. ETHICAL CONSIDERATIONS ..... Page 19
    - 8.1 Consent & withdrawal ..... Page 19
    - 8.2 Confidentiality ..... Page 20
    - 8.3 Data security ..... Page 20
    - 8.4 Data sharing ..... Page 20
    - 8.5 Ethical approval ..... Page 21
9. PARTICIPANT WITHDRAWAL/NON-CONSENT ..... Page 21
    - 9.1 Withdrawal of consent to all trial involvement ..... Page 21
    - 9.2 Withdrawal of consent for further data collection ..... Page 21
    - 9.3 Withdrawal of consent for data collection and use of existing data ..... Page 21
    - 9.4 Withdrawal of consent for sample analysis ..... Page 21
    - 9.5 Loss to follow up ..... Page 22
10. REFERENCES ..... Page 22

1. ABBREVIATIONS

CI	Chief Investigator
CRF	Case report form
CRP	C reactive protein
CT	Computed tomography
CXR	Chest radiograph
EQ-5D-5L	EuroQol 5D health questionnaire
FBC	Full blood count
FFPE	Formalin fixed paraffin embedded
FISH	fluorescent in situ hyberidisation
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
IPC	Indwelling pleural catheter
LFT	Liver function tests
MDT	Multidisciplinary team
Ml	Millilitres
MPM	Malignant pleural mesothelioma
NBT	North Bristol NHS Trust
NHS	National Health Service
PI	Principal Investigator
PIC	Participant identification centre
PIS	Participant information sheet
PROMs	Patient-reported outcome measures
PS	Performance status
QoL	Quality of life
RCT	Randomised controlled trial
REC	Research Ethics Committee
SOP	Standard operating procedure
TMA	Tissue microarray
TSC	Trial steering committee
TUS	Thoracic ultrasound scan
TWIC	Trial within a cohort
U&E	Urea and electrolytes
VAS	Visual analogue scale

2. STUDY SUMMARY

2.1 Plain English summary

Mesothelioma is an aggressive cancer that usually affects the outside lining of the lung but can also affect the lining of the heart or abdomen. It usually arises as a result of previous exposure to asbestos, often more than 40 years previously. Rates of mesothelioma diagnosis have increased steadily over the past decade, in the UK and worldwide, and are predicted to continue rising over the next 5-10 years.

Unfortunately the average life-expectancy of a person diagnosed with mesothelioma is less than a year. This is because it is very difficult to treat, with only one chemotherapy treatment that has been shown to be effective. On average, this chemotherapy allows people to live approximately 3 months longer, although some people respond really well and go on to live for many months or even years. Unfortunately at the moment, we can't predict which people will be the ones to respond well to chemotherapy. Lots of new treatments are being developed for mesothelioma, and many hospitals, including ours, are running clinical trials testing these treatments in willing patients.

We want to learn more about mesothelioma, specifically whether there are any patient characteristics, factors relating to the tumour or blood tests that will allow us to predict which patients might live longer. We also want to investigate whether there is any way of predicting which patients will respond well to chemotherapy. Finding this out will allow us to give patients more specific information about what they can expect of their disease and will help us make better treatment decisions for individual patients.

We will gather this information by setting up a database (cohort) of patients with mesothelioma diagnosed at our hospital, and at other hospitals in the UK. Patients who agree to join the cohort will provide clinical information at the point of diagnosis, alongside samples of blood and pleural fluid for analysis. Additional blood and pleural fluid samples will be kept, and stored anonymously, for further testing in the future. Participants will then continue to be followed up in clinic, as regularly as their treating consultant thinks necessary. At every clinic appointment, they will provide more information, for example about the severity of their current symptoms, which will be collected and added to the database. If possible, further samples of pleural fluid and blood will also be taken at these appointments. Participants will continue to provide information for the cohort at every pleural clinic appointment for the rest of their life.

The cohort will also be used as a resource for identifying patients who are suitable to participate in clinical trials. When they sign up to the cohort, participants will be asked whether they are willing to be invited to join clinical trials in the future. They will also be told that sometimes the decision to invite people to join a trial will be made by random selection. If they agree to this, then the data they provide to the cohort will also be used to assess their suitability for clinical trials, as and when they become available.

2.2 Scientific abstract

Mesothelioma is an aggressive malignancy of serosal surfaces that affects the pleura in the majority of cases, but can also affect the peritoneum or pericardium.[1] It arises as a result of pervious asbestos exposure, with a latency period of approximately 40 years between exposure and development of disease.[1 2] As a result of this time lag, mesothelioma incidence has risen

steadily over the past decade, and is predicted to continue, before reaching a peak in the next 5-10 years.[1 3-5]

Mesothelioma is currently incurable, and median survival is less than 1 year from diagnosis.[1 2 6-8] The only chemotherapy regimen that has been shown to be effective, cisplatin and pemetrexed doublet, offered a median survival benefit of just 2.8 months.[9] Recently, the addition of bevacizumab to this regimen extended median survival to 18.8 months, and this may become the new standard of care.[10 11] Numerous novel therapies are under investigation in clinical trials, including targeted monoclonal antibody agents and immunotherapy.[12-15]

The aim of this prospective study is to recruit patients with mesothelioma from multiple centres in the UK, to undergo regular observational follow up, providing data on the natural history of the disease, and the variation in outcomes depending on patient characteristics and treatment received. Sequential biological samples including blood and pleural fluid will be obtained and tested for various biomarkers to evaluate their diagnostic and prognostic accuracy. Additional biological samples will be stored for use as a biobank for future research studies.

The cohort will also provide a resource from which to conduct 'trials within a cohort' or 'TwiCs'.[16] This novel methodology offers a pragmatic and efficient alternative to the randomised controlled trial design by identifying eligible participants for a trial from an existing cohort, randomly selecting a proportion to receive the trial intervention, and using the ongoing cohort data from remaining participants as control data.

2.3 Study design

This is a prospective cohort study of patients diagnosed with mesothelioma, using a pragmatic, follow up schedule based on clinical requirements.

3. BACKGROUND

3.1 Mesothelioma

Mesothelioma is an aggressive cancer of the serosal surfaces that predominantly affects the pleura but can also affect the pericardium or peritoneum. It is associated with previous asbestos exposure, with a latency period of approximately 40 years between fibre exposure and disease presentation.[1 17-20]

Global incidence of mesothelioma has risen steadily over the past decade and is predicted to continue to an estimated peak in 2020.[1 17] Precise numbers are difficult to determine as the disease is likely to be underreported in areas of low incidence. However an estimate based on 2008 data suggested an average of 14,200 cases worldwide each year.[21] The UK has one of the incidences of mesothelioma, both in absolute numbers and cases per capita.[21 22]

Prognosis with MPM is poor and median survival ranges from 8 to 14 months from diagnosis.[1 3 17 18] Prognosis varies depending on the underlying tumour histology. There are four main histological sub-types; epithelioid, sarcomatoid, biphasic and desmoplastic. Sarcomatoid variant is associated with the worst outcomes, with median survival just 4 months. In contrast, epithelioid has the most favourable prognosis with a median survival of 13.1 months.[1 3 17]

Pharmacological therapy is the only treatment modality that has been shown to extend survival with mesothelioma. Chemotherapy with combination pemetrexed and cisplatin extended median

survival by 2.8 months compared with cisplatin alone in a phase 3 randomised trial.[9] Recently, the addition of the targeted anti-vascular endothelial growth factor (VEGF) antibody Bevacizumab to this regimen further extended survival to 18.8 months.[10] There are a number of investigational medicinal products in the pipeline for mesothelioma, including immunotherapy, gene therapy and mesothelin-targeted therapies. Clinical trials exploring the efficacy of these agents are underway in a number of centres.

3.2 Biomarkers and predictors of outcome

A biomarker is any molecule, gene or clinical characteristic that can be objectively measured and evaluated as an indicator of underlying pathological processes.[23] Biomarkers can be used to diagnose conditions, or to monitor progression and response to treatment. From a research point of view, biomarkers can provide mechanistic information to explain the empirical results of clinical trials, as well as providing potential surrogate markers for clinical endpoints.[23]

Unfortunately there is no diagnostic biomarker that offers acceptable diagnostic sensitivity and specificity in MPM.[24] [25] However, serum levels of the cell-adhesion glycoprotein mesothelin (also known as serum mesothelin related protein (SMRP)) may be of use prognostically in MPM, and may also predict tumour response following an intervention.[26] [27] However, the evidence supporting mesothelin as a prognostic marker is limited and further validation in larger cohorts is required.[28] Similarly, further investigation is warranted into pleural fluid mesothelin levels, which appear to correlate with serum mesothelin for diagnostic accuracy, but have not been investigated for prognostic purposes.[29]

The presence of pleural effusions in the majority of patients with MPM provides the opportunity for repeated sampling of fluid from the immediate tumour environment. Pleural fluid that has been aspirated for therapeutic purposes can provide important mechanistic or prognostic information following an intervention. This may be of particular use in the evaluation of immunotherapeutics, which often induce prolonged disease stability rather than tumour regression, and for which standard outcome measurements such as tumour dimensions on CT are less sensitive.[30] Serial pleural fluid samples can be used to assess pro-inflammatory cytokine levels as well as changes in immune cell populations in response to treatment. The ratio of neutrophils to lymphocytes (NLR) in blood has been shown to predict survival with MPM, and is able to identify patients who have responded well to chemotherapy.[31] [32] However it is not known whether pleural fluid can provide similarly useful information.

3.3 Justification for a mesothelioma cohort

As a rare disease, with variable geographical incidence, mesothelioma lends itself well to being studied in a cohort. The majority of cases are discussed at multidisciplinary team meetings, allowing rigorous identification of cases.

To date, in the UK, the National Lung Cancer Audit has collected information on all patients diagnosed with mesothelioma in secondary care. It is estimated to capture approximately 80% of the total incident cases.[3] This resource, which represents the largest published case series of people with MPM to date, has provided useful information on patient demographics, patterns of treatment and factors affecting survival. However, the Audit collects most of its information from MDT meetings and consequently the amount of information collected and, the degree of detail is limited by the time constraints associated with busy clinical practice. Longitudinal data is generally limited to detailing the treatment modalities received and overall survival. Serial data on symptoms and quality of life, repeated imaging and longitudinal biometric data were not

collected. Additionally, as a nationwide, electronic resource, biological samples could not be collected.

There is, therefore, a pressing need to collect longitudinal observational data in people with MPM, in order to explore the natural history of the disease. Collecting additional information in the form of biometric parameters and patient-reported outcomes will help clinicians understand the disease process better and allow them to provide more accurate information to patients in clinic. Finally, the storage of multiple biological samples will provide a resource for investigating and assessing potential biomarkers and predictors of clinical outcome.

3.4 The trial within a cohort design

The trial within a cohort (or 'TwiC') methodology is a highly pragmatic methodology that aims to remedy certain practical issues seen with the traditional randomised controlled trial (RCT) design.[16]

The methodology identifies participants who are eligible for a specific trial from within an existing cohort study. Eligible participants are randomly selected to be offered the trial intervention and are subsequently approached to discuss the trial and invited to consent to participate. Cohort participants who are eligible for the trial but are not allocated to the intervention arm remain in the cohort as controls and are not informed about the intervention.

The TwiC methodology offers certain benefits over traditional randomised controlled trial (RCT) design.[16] Cohort studies are associated with faster recruitment and more diverse participant characteristics, which is a benefit in MPM research, where recruitment can be slow and participant diversity narrow.[12 33]

TwiCs also offer the following specific advantages for MPM research:

- Chemotherapy has limited efficacy in MPM, and most patients do not receive it.[3] Consequently, many people participate in trials in the hope of gaining access to a treatment that is not otherwise available. However, if a trial includes a standard care arm, participants may decline randomisation or withdraw from the trial if allocated to this arm. Alternatively, they may feel disappointed, which could affect patient-reported outcomes. The TwiC design removes this issue, and may therefore reduce attrition bias and reporting bias.[16]

- In an RCT, participants are given information about all trial interventions and then randomly allocated to one. This differs from real-life clinical practice where patients are provided with information about treatment as and when they are going to receive it, and not if they are not going to receive it. TwiCs replicate this by providing information about the intervention solely to participants selected to receive it. This has two benefits: firstly it removes the ethical issue of informing a participant about an intervention that they only have a 50% chance of receiving, and secondly it increases the generalisability of the trial results by replicating real-life clinical care. It also creates a patient-centred consent process, whereby each participant provides consent for the exact treatment they will receive and none that they will not. This aligns well with the culture of open communication that exists between clinicians and patients with MPM.

- The TwiC methodology respects patients' choices to decline treatment. These participants would be excluded from an RCT but can participate in a TwiC and contribute observational data to the cohort.

- Using the TwiC design, participants in a cohort can be sampled repeatedly, allowing multiple trials to be undertaken, with shorter recruitment times. If this research demonstrates feasibility, further MPM trials can be undertaken from the same cohort. This could reduce recruitment times, reduce research costs and improve overall efficiency.

The TwiC methodology has been approved by ethics committees for use in intervention trials in patients with breast cancer, rectal cancer and metastatic bone disease[34] (see also https://clinicaltrials.gov/show/NCT02070146).

It is anticipated that the ASSESS-meso cohort will be used as a resource from which patients with MPM can be identified for future trials, and from which TwiCs will be conducted.

4. AIMS & OBJECTIVES

The aim of the cohort study is to establish a rolling cohort of patients with mesothelioma, in order to collect longitudinal data on the natural history of MPM, create a biobank of biological samples, and provide a resource for future TwiCs.

Specific objectives include the collection of longitudinal data across multiple domains including clinical, biochemical, biometric and psychological parameters. This data will provide information on the natural history of MPM and will allow comparison of outcomes in participants who undergo different management pathways. The collection and analysis of biological samples, including blood and pleural fluid, will allow investigation of novel biomarkers and exploration of other clinical and biochemical factors that influence outcome. Finally, longitudinal data collected in the cohort will provide control group data for TwiCs conducted within the cohort.

5. METHODOLOGY

5.1 Setting

The cohort will be established at 2 centres initially; North Bristol NHS Trust Pleural Service (NBT) and Oxford Respiratory Trials Unit (ORTU). Both of these centres have established track records in recruiting patients to mesothelioma trials and have appropriate research infra-structure in place to recruit to the cohort. The lead clinicians (Prof Nick Maskell at NBT and Prof Najib Rahman at ORTU) are experienced senior investigators with extensive clinical experience in pleural disease and MPM. Both centres hold dedicated pleural clinics, which receive regional referrals for MPM. Both centres also host regional mesothelioma multidisciplinary team (MDT) meetings in which new cases of MPM are discussed.

In addition to the two trial centres, there will be a number of participant identification centres (PIC) who refer patients for discussion at the regional mesothelioma MDT. These will include (but not be limited to) University Hospitals Bristol NHS Trust, Gloucester Hospitals NHS Foundation Trust, Weston Area Health NHS Trust, Taunton and Somerset NHS Foundation Trust, Yeovil District Hospital NHS Foundation Trust and Royal United Hospitals Bath NHS Foundation Trust.

Once approximately 100 participants have been recruited from these two centres, other centres will be invited to become recruiting centres for the study. It is anticipated that these additional centres will cover a wide geographical area across England.

5.2 Inclusion criteria

To be eligible to participate in the cohort, patients must meet all of the following criteria:

- Histological, cytological or clinico-pathological diagnosis of MPM, confirmed at MDT
- Willing and able to comply with study follow up assessments (including at least 1 appointment at a study recruiting centre if identified at a PIC)
- Willing & able to provide written informed consent

5.3 Exclusion criteria

To be eligible for the cohort, none of the following criteria should apply:

- Age <18 years old
- Unable to give written informed consent
- Declines ongoing hospital follow up

5.4 Screening, enrolment and consent

A member of the research team will attend the regional mesothelioma MDT each week to screen all patients newly diagnosed with MPM. Participants who meet the eligibility criteria (as stated in sections 5.2 and 5.3) will be invited to discuss the study with a member of the research team (CI, PI, research fellow or research nurse as named on the study delegation log) at their subsequent clinic appointment. The research team member will provide potential participants with a patient information sheet (PIS) and give them sufficient time to read it. Potential participants will have the opportunity to ask questions before being invited, by the researcher, to give consent to take part in the study.

Informed consent can be provided as written consent in person, or as witnessed verbal consent via telephone or virtual media (e.g. video-conferencing) For witnessed verbal consent, the participant must be seen and/or heard to express their agreement with each element of the consent form by two members of the research team. The research team members must then both sign the consent form in the appropriate section (see study specific procedure 1).

Detailed screening logs will be kept to record all cases of non-enrolment.

Participants will be asked to provide consent (written in person or witnessed verbal via telephone/ virtual software) for linked blood and pleural samples (if available) to be stored and analysed anonymously, at North Bristol NHS Trust (NBT). Participants from other centres will be asked to give their consent for samples to be transferred to NBT for storage and analysis. The researcher will also ask the participant to provide consent for data collected during the cohort study to be used as control data in future trials.

Participants who wish to have longer to consider the study or who are unable to complete the initial assessment due to time constraints will have the opportunity to return at a later date. There is no time limit between receiving a diagnosis of MPM and enrolling in the cohort. Once consent has been obtained, the researcher will complete the enrolment form and undertake the initial baseline assessments.

Participants who are being treated at a PIC who have been identified as eligible to participate in the cohort at the regional mesothelioma MDT, will be provided with a PIS and asked whether they are happy for a member of the research team to contact them to discuss the study. The clinician who has given them the PIS (consultant, registrar, junior doctor, specialist nurse, research nurse, clinic nurse or other member of the clinical care team) will be asked to inform the research team that they have given the patient a PIS, record whether the patient is happy to be contacted about the study and provide a contact telephone number for the patient. The person who gives the patient a PIS does not have to be a member of the research team and does not need to be named on the delegation log. Once the research team has been informed about a potential participant at a PIC, one of the research nurses will contact them by telephone and invite them to an appointment at their closest trial centre. If they accept, they will be seen by a member of the research team, given the opportunity to discuss the study and ask questions, before being invited to provide written or witnessed verbal informed consent. Eligible participants identified at PICs must be willing and able to travel to one of the study centres on at least one occasion. After this initial study visit, further study assessments can take place over the telephone if the participant does not wish to repeatedly attend the study centre.

5.5 Consent for future trials within the cohort

There will be a specific section on the consent form that relates to participation in future TwiCs. This will state "I am willing for my information to be used to identify other research trials that I am eligible for. I am willing to be chosen, on a random basis, to be invited to discuss these trials. I am aware that the decision to participate in future trials will be made at the time of discussion and does not need to be made now". A further section on the form will ask for participants to give their consent for data collected during ASSESS-meso to be used as control or comparison data for trials, even if they have not been selected to participate in that trial.

5.6 Sample size & recruitment targets

The sample size necessary to detect a difference in survival between different patient groups is 266 participants per group, i.e. 532 in total. Setting the recruitment target at 700 allows for approximately 20% withdrawals from the study, incomplete data and loss to follow up following initial enrolment. This calculation is based on the survival outcomes from previous chemotherapy trials in mesothelioma, in which chemotherapy increased 1 year survival from 38% to 50%.[9] With alpha of 0.05, a cohort of this size will provide 80% power to detect a similar difference in 1 year survival, based on an individual patient characteristics (split at the median) or treatment received (binary yes/no data).

NBT Pleural Service diagnoses approximately 50 new cases of MPM each year, whilst ORTU sees 30. It is anticipated that 90% of these people will be eligible to participate in the cohort.

Observational studies tend to have higher recruitment rates than interventional trials.[16] NBT Pleural Service has been recruiting patients with pleural disease to an observational study since 2008 (Investigating Pleural Disease, UKCRN 8960, REC reference 08/H0102/11), in which 80% of eligible patients screened consented to participate. Assuming similar rates for this cohort, approximately 50 patients will be recruited each year from the two lead centres. With these recruitment rates the study will recruit 700 participants in approximately 14 years. However, it is anticipated that after the first 100 participants have been recruited, additional study centres will be invited to join the cohort, thus expediting recruitment and ensuring it is completed within 10 years.

5.7 Co-enrolment guidelines

One of the primary aims of the cohort study is to establish a resource from which future TwiCs can be recruited. Therefore, participants in the cohort will be permitted to participate in other research studies and trials concurrent to their participation in the cohort. It is likely that this research will be co-ordinated and managed by either NBT or ORTU Pleural Teams, at least initially, but it is acknowledged that some patients may be invited to participate in oncological treatment trials or trials co-ordinated by other teams. There is no restriction on participation in any of these trials, provided the CI is informed at the time of co-enrolment, and is comfortable that there will be no conflict between studies. Co-enrolment will be documented on individual CRFs.

6. STUDY ASSESSMENTS

6.1 Baseline assessments

Having provided written or witnessed verbal informed consent to participate in the cohort, participants will undergo baseline assessment. This will include documentation of patient demographics (including whether or not they are living alone, their postcode, and alcohol history), disease characteristics, co-morbidities and medication history. Patient-reported outcome measures (PROMs) will be collected, specifically the EuroQol 5D health questionnaire, EQ-5D-5L and symptom scores for breathlessness, chest pain and sweats. For symptom scores, participants will be asked to assess the severity of the relevant symptom over the preceding 24 hour period and mark the score on a 10cm visual analogue scale (VAS). The overall duration of time patients have been experiencing symptoms will also be recorded.

Baseline blood tests will include full blood count (FBC), Urea and electrolytes (U&E), liver function tests (LFT), C reactive protein (CRP), lactate dehydrogenase (LDH), total protein, and random glucose. . If the participant has an indwelling pleural catheter in situ, drainage diaries will be reviewed and a sample of pleural fluid will be aspirated. Pleural fluid will be tested for protein, LDH, glucose and cytology. If the participant has an effusion that requires aspiration on clinical grounds, a sample of their fluid will be analysed for research purposes. Additional samples of blood and pleural fluid will be processed and stored for use in future research (see Section 6.7).

Participants will be asked to give consent for the research team to access the biopsy on which the diagnosis of mesothelioma was made. If there is sufficient tissue in the biopsy that is surplus to diagnostic or therapeutic requirements, the research team will obtain one or more samples of tissue from the biopsy for research purposes (see Section 6.7)

Thoracic ultrasound (TUS), chest x-ray (CXR) will be performed at baseline. The presence of trapped lung will be recorded. A computed tomography scan (CT) of the thorax should have been performed within 4 weeks of the baseline assessment, ideally with pleural phase contrast, although if a non-contrast scan has been performed within 4 weeks of the baseline assessment, this will suffice.

Eligible participants identified at PICs will be asked to attend one of the study centres on at least one occasion, to provide written or witnessed verbal informed consent and undergo baseline assessment once consent has been provided. In order to reduce inconvenience and increase

study participation, these participants will be offered the opportunity to undergo telephone follow up with reduced data collection, for ongoing study assessments.

6.2 Follow up assessments

Study assessments will be undertaken when the participant attends for review as part of standard clinical care. This should happen every 3 months as a minimum. Some participants will require more frequent follow-up for clinical reasons and will therefore undergo more frequent assessment. Participants who are eligible for participation in future TwiCs may be invited to attend more regular study assessments at one of the study centres, in accordance with the follow up schedule for that specific TwiC.

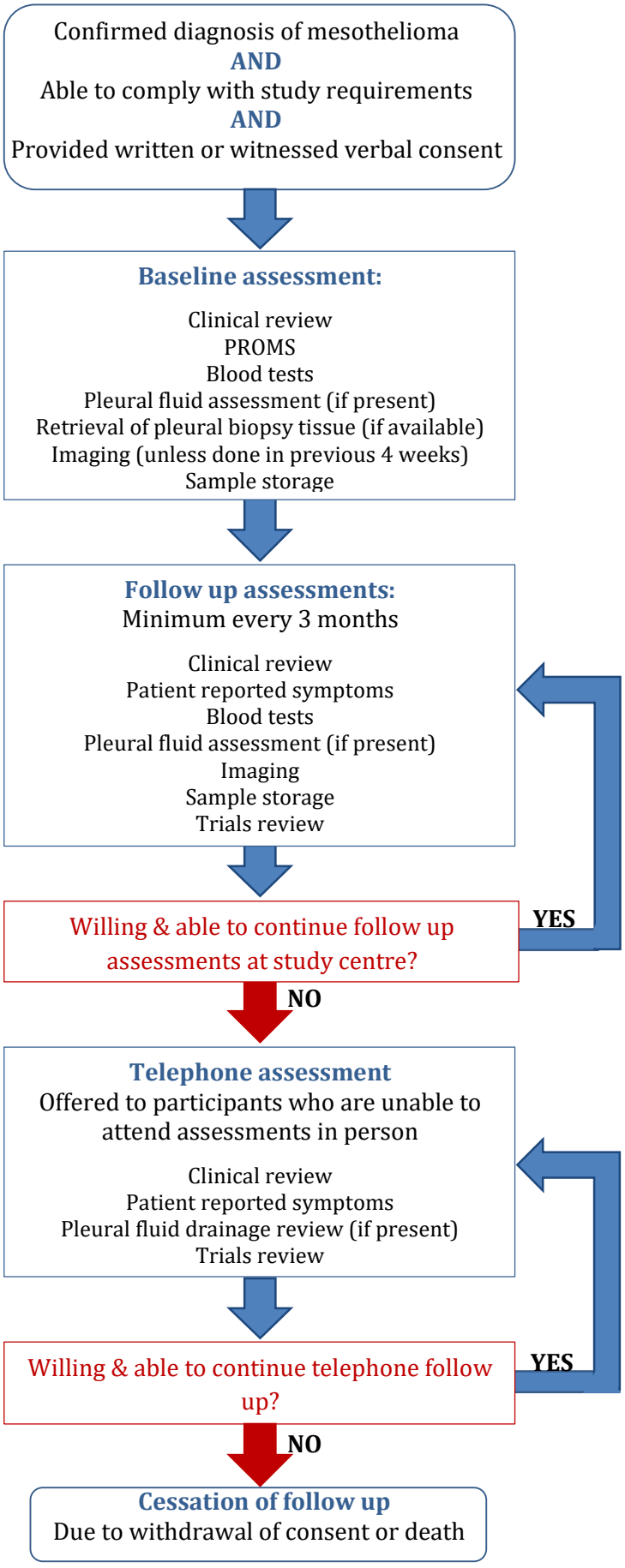
At each visit participants will undergo clinical assessment, including review of symptoms, medication history, oncological treatment received, details of any pain interventions, any engagement with Specialist Palliative Care teams and change in clinical status. Blood tests will be taken for FBC, U&E, LFT, CRP and random glucose,. A sample of blood will be taken for storage. Pleural fluid drainage diaries will be reviewed and documented. Participants who have an indwelling pleural catheter in situ or who are undergoing pleural aspiration for clinical reasons will have pleural fluid biochemistry tested and have a sample of pleural fluid taken for storage. Participants will complete PROMS for QoL and VAS scores for chest pain, breathlessness and sweats. Intermittently participants will be invited to complete daily VAS scores from home and will be provided with a VAS booklet to complete.

Radiological imaging, including CXR, CT thorax and bedside TUS will be undertaken at the discretion of the clinician, based on clinical need. It is anticipated that participants will have a CXR, TUS or both at every clinic appointment as part of routine care. It is expected that participants will have a CT scan every 6 months as a minimum for routine clinical care. If a participant has more frequent CT scans, for clinical reasons, these images will be collected as part of the study.

At each follow up assessment, cohort participants will be assessed for their eligibility to participate in any trials (TwiCs) that are currently underway within the cohort. Any participant who meets the eligibility criteria for a TwiC will be provided with a PIS for that trial and given the opportunity to discuss it with a member of the trial team. As part of the screening process, additional blood samples or investigations may be undertaken to determine or confirm eligibility for specific trials. These activities are deemed ASSESS-meso

Participants in ASSESS-meso who are enrolled in, have completed or are providing control data for a TwiC will undergo adverse event monitoring at each ASSESS-meso visit. This is to ensure ongoing safety monitoring for participants who have participated in CTIMPs, and to allow collection of data on any late-presenting complications.

6.3 **Study flow diagram**



6.4 Schedule of assessments

Description	Investigation	Baseline assessment	Follow up assessment	Telephone assessment
Clinical review	Patient demographics	X		
	Disease characteristics	X		
	Patient co-morbidities	X		
	Assessment of PS	X	X	
	Medication history	X	X	X
	Oncological treatment history	X	X	X
	Pleural intervention history	X	X	X
PROMS	Breathlessness VAS	X	X	X
	Chest pain VAS	X	X	X
	Sweats VAS	X	X	X
	EQ-5D-5L QoL score	X	X	X
Blood tests	FBC	X	X	
	U&E	X	X	
	LFT	X	X	
	CRP	X	X	
	LDH	X	X	
	Total protein	X	X	
	Random glucose	X	X	
	CMV IgM/IgG	X*		
	White blood cell phenotyping	X*		
	CMV viral load	X*		
Imaging	TUS	X	X+	
	CXR	X	X+	X+
	CT Thorax (minimum every 6 months)	X	X+	X+
Pleural fluid assessment (if present)	Total protein	X*	X*	
	LDH	X*	X*	
	Glucose	X*	X*	
	Cytology	X*	X*	
	Review of drainage diaries	X*	X*	X*
Pleural biopsies (if available)	Retrieval of FFPE sample from pathology services	X		
	Core samples stored for TMA	X		
	Unprocessed sample(s) stored in RNA Later	X		
Pleural biopsies tests (if available)	Immunohistochemical and FISH testing of protein and genetic markers	X*		
	Histological assessment of grade, necrosis and other prognostic factors	X*		
Storage of samples	Blood sample for storage	X	X	
	Pleural fluid for storage	X	X	
Trial review	Assessment of eligibility for any current trials, including screening blood tests	X	X	X*
	Documentation of trial participation	X	X	X*
Consent	Verbal consent for ongoing participation		X	X

X = required **X* = if applicable** **X+ = at clinician's discretion, ideally every 4 months**

6.5 Telephone/postal assessments

Participants who are unable to attend regular study follow up appointments, either as a result of frailty or geographical distance from a study centre (including participants identified from PICs), may undergo telephone or postal follow up. Telephone appointments will be undertaken by a research nurse, or any member of the research team. Assessments will include a brief clinical review covering any oncological treatments received or pleural procedures undergone since the previous assessment, and review of pleural fluid drainage diaries for participants who have an IPC in situ. Symptoms will be reviewed, and EQ-5D-5L QoL questionnaire and VAS scores will be completed verbally. Alternatively VAS scores and QoL questionnaires may be sent through the post for completion by the participant in their own time. Assessment of eligibility for trials will be undertaken, if appropriate.

Participants who are undergoing telephone assessments and wish to be considered for clinical trials must be willing and able to attend trial visits at the appropriate trial centre.

6.6 Questionnaires & patient reported outcomes

Participants will complete the EQ-5D QoL questionnaire at every trial visit. The EQ-5D-5L is a widely used preference-based generic health-related QoL instrument and is the instrument favoured by the National Institute of Health and Care Excellence (NICE).[35] It measures QoL on 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with 3 severity levels for each dimension, producing a possible 243 health states. A utility score can be generated for each health state by applying country-specific general population-elicited tariffs, which can then be used to calculate quality-adjusted life years. This data set used the UK population EQ-5D-5L tariff.[36] EQ-5D-5L has been applied to mesothelioma in clinical trials of surgical interventions, radiotherapy and palliative care, as well as being used in previous mesothelioma cohort studies.[37-40]

Patient reported symptoms of breathlessness and chest pain will be recorded at each study visit. Symptoms will be reported on a 10cm VAS with anchored at zero - “no pain/breathlessness” and 10 “worst pain/breathlessness imaginable”. VAS are a validated tool for assessing breathlessness and chest pain in malignant pleural disease and are acceptable to patients.[41 42] Despite being a well-recognised symptom of mesothelioma, the frequency and severity of sweating has not been evaluated in patients with mesothelioma before. Its inclusion in the cohort assessment is a result of patient feedback during a public engagement event. It is hoped that collecting this data will provide information into the prevalence of this symptom and its relationship to survival and other clinical outcomes. The VAS for sweating will be similar to the VAS for pain and breathlessness and will be based on existing VAS used to assess hyperhidrosis and associated conditions.

6.7 Biological samples

Participants will be asked to give their consent for blood and pleural fluid samples to be collected and stored for use in the current study and future research, both in the UK and overseas. Consent will also be requested for access to surplus biopsy tissue, not required for diagnostic or therapeutic purposes. A hierarchy of access will be followed to ensure that local clinical diagnostic services have first access to tissue, with ASSESS-meso receiving additional tissue only if it is available.

Certain tests (e.g. blood haematology and biochemistry, pleural fluid biochemistry, and flow cytometry) will be run on the day the sample is obtained. Blood analysis for circulating tumour cells will be analysed according to study specific procedure 12 – sample processing for UBC sub-study. Further blood and pleural fluid samples will be stored for future analyses, including but not limited to cytokine levels, immune cell population assessment and phenotyping, tumour metabolites and receptor status, and epigenetic biomarkers to assess for any associations with progression of disease and mortality.

Additional DNA extraction and genetic analysis will be performed on blood, pleural fluid and tissue samples where the study participants have provided their consent to allow this.

Biological samples will be collected by research nurses, clinicians and members of the study team as required for routine clinical care. Research samples will be processed and stored as described in the relevant study specific procedures. All samples will be stored anonymised, identifiable by ASSESS-meso study number and a study specific bar-code only. The code sheet will be stored securely, in a separate location to the samples.

Study specific procedure documents will be provided to all sites involved in the processing and storage of biological samples,

Study samples may be sent to laboratories outside of the trial centres (including overseas) for processing and for tests to be performed. All samples sent for analysis, and any data sent with the samples, will be anonymised and labelled with the ASSESS-meso study number. Samples will be transported by first class post in accordance with UN 3373 regulations, under the classification Biological substance, Category B. All samples will be transported in compliance with 49 CFR, Part 173.199 and/or IATA Packing Instruction 650 approved regulations.

Samples will be stored, with participants' consent, at local sites prior to batch transport to North Bristol NHS Trust. Participants will be asked to consent to storage of their samples and for their samples to be used in other research studies and/or shared with other researchers (including overseas), once ASSESS-meso has finished.

6.7.1 Biopsy samples

A sample of diagnostic biopsies will be retrieved as described in 6.1. These will be assessed histologically for nuclear grade, necrosis and other prognostic factor, and undergo immunohistochemical and FISH testing of protein and genetic markers.

6.8 Cessation of follow up

Follow up assessments will cease if the participant withdraws from the study, or if the participant dies. The research team will receive regular cancer/death notifications from the NHSCR and the NHSIC. The registers will notify us of subsequent cancer registrations and mortality among cohort members throughout the study. Where sites have become aware that a patient has died, they will notify the ASSESS-meso team. A mortality form will be completed for each deceased patient.

It is possible that participants will become increasingly frail as they approach the end of their life, and the demands of ongoing cohort follow up may be too onerous for them. These participants should be offered the longest interval between study assessments (i.e. 4 months). If this schedule still proves too burdensome, then they will be invited to participate in telephone follow up. If they do not wish to do this, they will be invited to withdraw from the study. They will be asked whether they are happy for their existing data and biological samples to be kept as part of the

study. They will also be asked whether they consent to a member of the research team accessing their medical records via online registries to determine date of death. Further information on withdrawal from the study is described in Section 9.

6.9 Study duration

The cohort study will run for 10 years or until a total of 700 participants have been recruited, whichever happens first. Participants who consent to join the cohort will remain under follow up until death, or withdrawal from the study. Since median life expectancy with MPM is approximately 1 year from diagnosis, it is anticipated that the cohort population will be dynamic, and the cohort will be a continuously "rolling" as new participants are enrolled, and other participants leave the cohort, either as a result of withdrawal or mortality.

6.10 Source data

The primary data source will be the participant's medical notes. The laboratory reports will form the primary data source for blood results. The CT scan report will form the primary data source for any scans. Patient-reported outcome measures, such as symptoms, quality of life and pleural fluid drainage, will use the individual participants' diaries as source data.

Electronic case report forms (CRFs) will be used to collect data at each study visit. Paper check-lists will be provided to each study centre to use as a prompt for electronic CRFs if desired. Completed checklists are not classified trial documents and can be filed in the patients' notes to act as source data or stored or destroyed at the respective study centre. At the end of the study, all essential documents will be archived locally by participating sites, in accordance with NBT's archiving SOP (RI/QMS/SOP/010, available at https://www.nbt.nhs.uk/sites/default/files/sites/default/files/RI%20QMS%20SOP%20010%20-%20Archiving.pdf).

7. STATISTICAL ANALYSIS PLAN

We will use multiple linear regression to compare continuous outcomes; logistic regression to compare dichotomous outcomes and Cox's proportional hazards to compare survival between different groups controlling for confounding factors. We will use random effects models or robust estimates to allow for clustering between centres. Outcomes with repeat measurements will be analysed using regression modelling with adjustment for baseline values.

The sensitivity, specificity, NPV and PPV for predicting disease progression will be assessed at established cut-off levels for serum and pleural fluid biomarkers, cytokines, immune profile, receptor status and epigenetic markers. Receiver operator characteristic curves will be drawn. The gold standard for disease progression will be confirmation of progressive disease made at the regional mesothelioma MDT meeting.

An interim analysis will be undertaken once recruitment reaches 25% of target (i.e. n=175), describing the baseline characteristics of participants, and evaluating generalisability of the cohort population with comparison to existing real-world cohorts, e.g. National Lung Cancer Audit Mesothelioma Report.

8. ETHICAL CONSIDERATIONS

8.1 Consent & withdrawal

Participants must have full capacity to provide consent for the study, as defined by the Mental Health Capacity Act 2005. The consent form will specifically refer to the use of participants' data to identify additional trials they may be eligible for, and that they may be randomly selected to be invited to join such trials in future. Participants who have not consented to this element will not be eligible for future TwiCs. Participants will also be asked to provide consent for biological samples to be stored, anonymously, and analysed as part of future research trials.

The right of the participant to refuse to participate in the study without giving a reason is respected. Similarly, participants remain free to withdraw at any time from study follow-up without giving reasons and without prejudicing their further treatment. These participants' existing data will remain within the cohort unless the participant has specifically withdrawn consent for such follow-up. See section 9 for further information about withdrawal of consent.

8.2 Confidentiality

Study staff will ensure that participants' anonymity is upheld by secure handling and storage of patient information at research centres. All study documents will be stored securely and will be accessible only to study staff and authorised personnel. Data will be collected and retained in accordance with the Data Protection Act 1998.

Participants' personal data will be treated as strictly confidential. To maintain anonymity, only participants' study number, initials and date of birth will be recorded on study documentation. Participants' data will be stored on an administrative Access database. The database will be stored on a secure University of Bristol server and will be protected by a combination of file permissions and passwords. Only authorised study team members will have access to participants' personal data. The local researcher at each centre will be responsible for entering personal participant information into the database and allocating their study number.

8.3 Data security

Anonymised study data will be stored using a bespoke, online, secure database. Researchers at study centres will enter participant data onto electronic CRFs within the database. The database will include real-time queries to reduce missing or impossible data and optimise data quality.

Trial centres will be provided with paper "crib-sheets" to provide prompts for the electronic CRFs. These crib-sheets will be retained at each study centre, in secure storage, and will be made available on request to the sponsor for audit purposes. At the end of the study, all essential documents, including patient records and CRFs will be sent to NBT for archiving. Archiving will take place in accordance with NBT's archiving SOP.

Electronic records will be protected using a combination of passwords and file permissions. Data procedures will adhere to the Data Protection Act 2000. Electronic data will be retained and, at the end of the study, archived in line with Trust policy. With participants' consent, electronic research data will be stored indefinitely and made available for future analysis.

8.4 Data sharing

In line with NIHR guidance which encourages the sharing of anonymised datasets, participants will be asked to provide consent for their data to be shared with other researchers. This is in anticipation that data sharing and access to anonymised datasets may become mandatory in the coming years.

The data of participants who agree for their anonymised data to be shared will be stored on the University of Bristol Research Data Storage Facility at the end of the study. This data will then be shared, via the University of Bristol Research Data Repository, with other researchers once a Data Access Agreement has been signed by an institutional signatory. Participants who decline to have their data shared can still participate in the study; their data will be removed from the dataset prior to archiving for potential sharing.

8.5 Ethical approval

The study protocol will be submitted to the Health Research Authority (HRA) for Research Ethics Committee (REC) approval. The study consent form, participant information sheets and letter to inform their General Practitioner (GP) that they are participating in the study will be submitted to the HRA for approval at the same time. Full HRA approval will be in place before the trial commences.

9. PARTICIPANT WITHDRAWAL/NON-CONSENT

All participants will provide written or witnessed verbal informed consent to trial follow-up and to sample collection, storage and analysis where appropriate. Participants have the right to withdraw consent at any point. Withdrawal does not have to be justified and will not affect future or on-going care.

Participants will be asked, at every study assessment visit, whether they wish to continue participating in the study. If they do not wish to continue face-to-face assessments, they will be offered telephone follow up or alternatively, will be offered withdrawal from the study. If they wish to withdraw, they will be provided with the different withdrawal options as listed below.

In the event of withdrawal, any details available for the reason(s) will be recorded in the patient's electronic CRF, alongside documentation of the nature of consent withdrawal, as outlined below. Patients may still be classified as 'alive' or 'dead' at the end of their follow-up period unless consent for clinical data use is withdrawn.

9.1 Withdrawal of consent to all trial involvement

The participant withdraws consent for all study involvement, including further data collection, sample storage and analysis, and the use of data already collected in the final trial analysis (excluding data already used in published reports). Samples already taken and follow-up data should be destroyed as per local policy.

9.2 Withdrawal of consent for further data collection

The participant withdraws consent for further follow-up visits and recording of clinical data. They maintain consent for blood and fluid samples already taken to be analysed, and for data already collected to be used in future analyses.

9.3 Withdrawal of consent for further data collection and use of existing data

The participant withdraws consent to further follow-up visits, recording of clinical data and the use of any clinical data already collected (excluding data already used in published reports). They maintain consent for blood and fluid samples already taken to be analysed.

9.4 Withdrawal of consent for sample analysis

The participant withdraws consent for existing blood and pleural fluid samples to be analysed, and for any data already obtained from these samples to be used in the final analysis. Samples and associated data should be destroyed in line with local policy. They maintain consent for ongoing trial follow-up, data collection and the use of this data in the final analysis.

9.5 Loss to follow up

Loss to follow up will be minimised by diligent liaison with the patient, their oncology team and their GP. Any loss to follow-up should be recorded on the participant withdrawal/loss to follow-up form. For participants moving from the area, every effort should be made for the participant to be followed up at another centre, or for follow up via their GP.

10. REFERENCES

1. British Thoracic Society Standards of Care C. BTS statement on malignant mesothelioma in the UK, 2007. *Thorax* 2007;62 Suppl 2:ii1-ii19.
2. Ribak J, Selikoff IJ. Survival of asbestos insulation workers with mesothelioma. *British journal of industrial medicine* 1992;49(10):732-35.
3. Beckett P, Edwards J, Fennell D, et al. 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):344-8.
4. Riaz SP, Coupland VH, Luchtenborg M, et al. Mesothelioma incidence projections in South East England. *European Respiratory Journal* 2012;40(4):965-8.
5. Peake MD BP, Woolhouse I, et al on behalf of the National Lung Cancer Audit Project Team. National Lung Cancer Audit Report 2014, mesothelioma. Report for the period 2008–2012 http://www.hscic.gov.uk/media/15038/Mesothelioma-audit/pdf/EMBARGOEDTO120914_NLCA_Meso_Report_final.pdf: Health & Social Care Information Centre; 2014 [accessed 21/1/15 2015.
6. Linton A, Pavlakis N, O'Connell R, et al. Factors associated with survival in a large series of patients with malignant pleural mesothelioma in New South Wales. *British Journal of Cancer* 2014;111(9):1860-9.
7. Hodgson J, McElvenny D, Darnton A, et al. The expected burden of mesothelioma mortality in Great Britain from 2002 to 2050. *British journal of cancer* 2005;92(3):587-93.
8. Rudd RM. Malignant mesothelioma. *British Medical Bulletin* 2010;93(1):105-23. doi: 10.1093/bmb/ldp047
9. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003;21(14):2636-44.
10. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a

randomised, controlled, open-label, phase 3 trial. *The Lancet*;387(10026):1405-14. doi: http://dx.doi.org/10.1016/S0140-6736(15)01238-6
11. Zauderer MG. A new standard for malignant pleural mesothelioma. *Lancet* 2016;387(10026):1352-4.
12. Calabro L, Morra A, Fonsatti E, et al. Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial. *Lancet Oncology* 2013;14(11):1104-11.
13. Calabrò L, Morra A, Fonsatti E, et al. Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study. *The Lancet Respiratory Medicine* 2015;3(4):301-09. doi: http://dx.doi.org/10.1016/S2213-2600(15)00092-2
14. Kindler HL. Systemic treatments for mesothelioma: standard and novel. *Current treatment options in oncology* 2008;9(2-3):171-9. doi: 10.1007/s11864-008-0071-3
15. Nowak AK, Lesterhuis-Vasbinder D, Lesterhuis WJ. New directions in mesothelioma treatment. *Lung Cancer Management* 2015;4(6):299-307. doi: 10.2217/lmt.15.32
16. Relton C, Torgerson D, O'Cathain A, et al. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. *Bmj* 2010;340:c1066.
17. Scherpereel A, Astoul P, Baas P, et al. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. *European Respiratory Journal* 2010;35(3):479-95. doi: 10.1183/09031936.00063109
18. Yates D, Corrin B, Stidolph P, et al. Malignant mesothelioma in south east England: clinicopathological experience of 272 cases. *Thorax* 1997;52(6):507-12.
19. Howel D, Arblaster L, Swinburne L, et al. Routes of asbestos exposure and the development of mesothelioma in an English region. *Occupational and Environmental Medicine* 1997;54(6):403-09. doi: 10.1136/oem.54.6.403
20. Sekido Y. Molecular pathogenesis of malignant mesothelioma. *Carcinogenesis* 2013;34(7):1413-19. doi: 10.1093/carcin/bgt166
21. Park F-K, Takahashi K, Hoshuyama T, et al. Global magnitude of reported and unreported mesothelioma. *Environmental health perspectives* 2011;119(4):514.
22. Kazan-Allen L. Asbestos and mesothelioma: Worldwide trends. *Lung Cancer* 2005;49, Supplement 1:S3-S8. doi: http://dx.doi.org/10.1016/j.lungcan.2005.03.002
23. Biomarkers Definitions Working G. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clinical Pharmacology & Therapeutics* 2001;69(3):89-95. doi: 10.1067/mcp.2001.113989
24. Hollevoet K, Reitsma JB, Creaney J, et al. Serum mesothelin for diagnosing malignant pleural mesothelioma: an individual patient data meta-analysis. *J Clin Oncol* 2012;30(13):1541-49.
25. Hooper C, Lee YC, Maskell N, et al. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. *Thorax* 2010;65 Suppl 2:ii4-17.
26. Hassan R, Remaley AT, Sampson ML, et al. Detection and Quantitation of Serum Mesothelin, a Tumor Marker for Patients with Mesothelioma and Ovarian Cancer. *Clinical Cancer Research* 2006;12(2):447-53. doi: 10.1158/1078-0432.ccr-05-1477
27. Linch M, Gennatas S, Kazikin S, et al. A serum mesothelin level is a prognostic indicator for patients with malignant mesothelioma in routine clinical practice. *BMC Cancer* 2014;14(1):1-7. doi: 10.1186/1471-2407-14-674
28. Bonotti A, Simonini S, Pantani E, et al. Serum mesothelin, osteopontin and vimentin: useful markers for clinical monitoring of malignant pleural mesothelioma.0. doi: 10.5301/jbm.5000229
29. Cui A, Jin X-G, Zhai K, et al. Diagnostic values of soluble mesothelin-related peptides for malignant pleural mesothelioma: updated meta-analysis. *BMJ open* 2014;4(2):e004145.
30. Hoos A, Eggermont AMM, Janetzki S, et al. Improved Endpoints for Cancer Immunotherapy Trials. *Journal of the National Cancer Institute* 2010 doi: 10.1093/jnci/djq310

31. Kao SC, Pavlakis N, Harvie R, et al. High blood neutrophil-to-lymphocyte ratio is an indicator of poor prognosis in malignant mesothelioma patients undergoing systemic therapy. *Clinical Cancer Research* 2010;16(23):5805-13.
32. Yamagishi T, Fujimoto N, Nishi H, et al. Prognostic significance of the lymphocyte-to-monocyte ratio in patients with malignant pleural mesothelioma. *Lung Cancer* 2015;90(1):111-17. doi: http://dx.doi.org/10.1016/j.lungcan.2015.07.014
33. O'Brien ME, Watkins D, Ryan C, et al. A randomised trial in malignant mesothelioma (M) of early (E) versus delayed (D) chemotherapy in symptomatically stable patients: the MED trial. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2006;17(2):270-5. doi: 10.1093/annonc/mdj073
34. Burbach JM, Verkooijen HM, Intven M, et al. RandomizEd controlled trial for pre-operAtive dose-escaLation BOOST in locally advanced rectal cancer (RECTAL BOOST study): study protocol for a randomized controlled trial. *Trials* 2015;16(1):1.
35. Longworth L, Rowen D. Mapping to obtain EQ-5D utility values for use in NICE health technology assessments. *Value in Health* 2013;16(1):202-10.
36. Dolan P. Modeling valuations for EuroQol health states. *Medical care* 1997;35(11):1095-108.
37. Rintoul RC, Ritchie AJ, Edwards JG, et al. Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. *The Lancet*;384(9948):1118-27. doi: 10.1016/S0140-6736(14)60418-9
38. Clive AO, Taylor H, Dobson L, et al. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet Oncol* 2016 doi: http://dx.doi.org/10.1016/S1470-2045(16)30095-X
39. Gunatilake S, Brims FJ, Fogg C, et al. A multicentre non-blinded randomised controlled trial to assess the impact of regular early specialist symptom control treatment on quality of life in malignant mesothelioma (RESPECT-MESO): study protocol for a randomised controlled trial. *Trials [Electronic Resource]* 2014;15:367.
40. Arnold DT, Hooper CE, Morley A, et al. The effect of chemotherapy on health-related quality of life in mesothelioma: results from the SWAMP trial. *British Journal of Cancer* 2015;112(7):1183-9.
41. Mishra EK, Corcoran JP, Hallifax RJ, et al. Defining the minimal important difference for the visual analogue scale assessing dyspnea in patients with malignant pleural effusions. *PLoS ONE [Electronic Resource]* 2015;10(4):e0123798.
42. Mishra EK. Measurement of breathlessness in patients with malignant pleural effusions. *Current Pulmonology Reports* 2016;5(1):1-6. doi: 10.1007/s13665-016-0130-3
43. Cleeland CS RK. Pain assessment: Global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994;23(2):129-38.
44. Portenoy RK PD, Jacobsen P. Breakthrough pain: Characteristics and impact in patients with cancer pain. *Pain* 1999;81(1):129-34.
45. Zigmond AaSR. The hospital anxiety and depression scale. . *Acta Psychiatrica Scandinavica* 1983;67(6):361-70.
46. Hopwood P HA, and Maguire P. Screening for psychiatric morbidity in patients with advanced breast cancer: validation of two self-report questionnaires. . *British Journal of Cancer* 1991;64(2):353-6.
47. Groenvold M PM, Aaronson NK, et al. . The development of the EORTC QLQ-C15-PAL: a shortened questionnaire for cancer patients in palliative care. *Eur J Cancer* 2006;42(1):55-64.