Mesothelioma and Radical Surgery 2: a multicentre randomised trial comparing (extended) pleurectomy decortication versus no (extended) pleurectomy decortication for patients with malignant pleural mesothelioma

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Table of contents

Glossary / abbreviations

AE	Adverse event - any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.
AR	Adverse reaction – any undesirable experience that has happened a subject while taking a drug that is suspected to be caused by the drug or drugs
BRI	Bristol Royal Infirmary
BRU	Biomedical Research Unit
BTC	Bristol Trials Centre
CI	Chief Investigator
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CT	Computed tomography
CTEU	Clinical Trials and Evaluation Unit
DMSC	Data monitoring and safety committee
ECOG	Eastern Cooperative Oncology Group
FEV	Forced expiratory volume
FEV_1	Forced expiratory volume after one second
HRA	Health Research Authority
HRQoL	Health related quality of life
ICH-GCP	International conference for harmonisation of good clinical practice
MDT	Multidisciplinary team
MHRA	Medicines and healthcare products regulatory agency
MI	Myocardial infarction
NIHR	National Institute for Health Research
PIL	Patient information leaflet
PPI	Patient and public involvement
QA	Quality Assurance
QRI	QuinteT recruitment intervention
RCT	Randomised controlled trial
REC	Research ethics committee
SAE	Serious adverse event - events which result in death, are life threatening, require hospitalisation or prolongation of hospitalisation, result in persistent or significant disability or incapacity.
SAR	Serious adverse reaction
SOP	Standard operating procedure
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction - an untoward medical occurrence suspected to be related to a medicinal product that is not consistent with the applicable product information and is serious.
TIA	Transient ischemic attack
TMG	Trial management group
TSC	Trial steering committee
VATS	Video-assisted thoracoscopic surgery

1. Trial summary

In the UK, around 2,500 patients are diagnosed yearly with pleural mesothelioma, a cancer of the lining of the chest wall and lung mainly due to previous (40 to 60 years ago) exposure to asbestos. Mesothelioma does not respond well to chemotherapy and is an extremely lethal form of cancer (half of patients in the UK die within 8.5 months of diagnosis), therefore surgery to remove as much of the disease as possible, is often considered as one of the most important treatment options.

The only two surgical trials performed to date (both conducted in the UK) found that neither extensive surgery (removing all disease in chest and entire lung - extra-pleural pneumonectomy) nor limited surgery (removing some disease in the chest - partial pleurectomy) led to any improvement in survival, although there was some evidence of improved quality of life. Pleurectomy decortication is an intermediate form of surgery which removes disease in the chest but not the lung, but we do not know if this will prolong length of life and it continues to be offered in an ad hoc and patchy manner in the UK (and worldwide) due to absence of high quality evidence of clinical efficacy.

The MARS 2 trial will compare surgery - (extended) pleurectomy decortication - versus no surgery with respect to overall survival in patients with pleural mesothelioma. Patients deemed suitable for surgery will be approached and participants will receive 2 cycles of chemotherapy and a computed tomography (CT) scan. If there is no significant worsening of cancer, participants will be randomised to either surgery and 4 further cycles of chemotherapy or no-surgery and 4 further cycles of chemotherapy. The trial is designed to detect a 30% relative difference in survival. An economic evaluation will be undertaken and experts in trial recruitment will be working closely with the trial team to optimise recruitment and informed consent. A pilot trial recruited over 50 patients and we aim to recruit a further 88 patients per year to complete total recruitment of 328 participants within the next 3 years.

2. Background

Approximately 2,500 patients are diagnosed each year in the UK with pleural mesothelioma, a treatment resistant and extremely lethal cancer of the lining of the chest wall due to asbestos exposure. Deaths are increasing yearly and estimated to peak in 2020.(1) So far, most treatments have proven ineffective. The current standard of care, consisting of 6 cycles of platinum and pemetrexed chemotherapy as recommended by NICE, was associated with only an additional 3-month survival improvement.(2)

In a disease with a median UK survival of 8.5 months, surgery that is offered to 27% of patients in the UK remains an important consideration to improve length and/or quality of life.(3)

There are three main operations for pleural mesothelioma in decreasing order of extent of surgical resection, i) extra-pleural pneumonectomy - removal of the lining of the chest wall, lining of the lung, the lung itself with the sac around the heart and / or diaphragm (as required to achieve complete tumour removal), ii) pleurectomy decortication - removal of the lining of the chest wall, lining of the lung, and considered “extended” if the sac around the heart and / or diaphragm is removed to achieve complete tumour removal, but the lung is left in-situ and iii) partial pleurectomy – removal of part of the lining of the chest wall and lining of the lung only.

The UK mesothelioma research community is the only research group in the world to have recruited over 246 patients and completed and published two randomised trials of surgery for mesothelioma (MARS 1 and MesoVATS), and the work has influenced mesothelioma practice worldwide. MARS 1 concluded extra-pleural pneumonectomy offered no benefit (survival or quality of life) and possibly harms patients (4), in 2013/14 the operation accounted for less than 2% of surgical procedures undertaken for mesothelioma in the UK (5), a testament to the practice changing influence of the UK conducted clinical trial. MesoVATS concluded that partial pleurectomy did not improve survival, with some evidence that patients in the surgery arm had better quality of life at 6 months.(6)

But we do not know if pleurectomy decortication (the most common surgical procedure for mesothelioma worldwide) in conjunction with chemotherapy will improve length of life compared to chemotherapy alone (current standard of care). In the absence of randomised trials, pleurectomy decortication will continue to be offered despite lack of high-quality evidence of clinical efficacy or any evidence on cost-effectiveness.

Currently, the UK and international mesothelioma communities routinely offer pleurectomy decortication to suitable patients with mesothelioma, as it is considered to carry less morbidity compared to the more extensive extra-pleural pneumonectomy whilst achieving better cancer clearance compared to the lesser surgical extent of a partial pleurectomy operation.(7-9)

In the fiscal year 2013/4, the Society for Cardiothoracic Surgery's Thoracic Surgery Database reported 120 patients with mesothelioma undergoing surgery with "therapeutic" intent, 2 underwent extra-pleural pneumonectomy and the vast majority of the remaining 118 underwent pleurectomy decortication (the number of patients undergoing partial pleurectomy alone was not well documented).(5)

A systematic review of pleurectomy decortication for mesothelioma was published in 2013 by Cao et al; of 34 published case series of 1,916 patients concluding similar perioperative mortality outcomes between different series.(10) As there were no comparative no-surgery arms, the authors could not make any estimates of treatment efficacy of the technique. A systematic review of lung sparing extirpative surgery for mesothelioma was published in 2010 by Teh et al of 26 published case series involving 1270 patients.(9) The authors confirmed in the absence of any form of control data, no conclusions can be drawn concerning survival differences or symptomatic benefits attributable to surgery.

3. Rationale

The MARS 2 trial will inform if (extended) pleurectomy decortication is a clinical and / or cost-effective therapeutic intervention for patients with mesothelioma which is important to inform NHS practice, health policy and individual surgeon and patient clinical decision-making. On the other hand, if the trial results refute our hypothesis of clinical efficacy, the operation is unlikely to be routinely offered, eliminating procedure related complications for patients and reducing potential treatment costs of £766,174 per year for the NHS (118 procedures annually x £6,493 average NHS treatment cost).

4. Aims and objectives

To compare the effectiveness and cost-effectiveness of (extended) pleurectomy decortication versus no (extended) pleurectomy decortication for treatment of pleural mesothelioma. To test the hypothesis that (extended) pleurectomy decortication and chemotherapy is superior to chemotherapy alone with respect to overall survival.

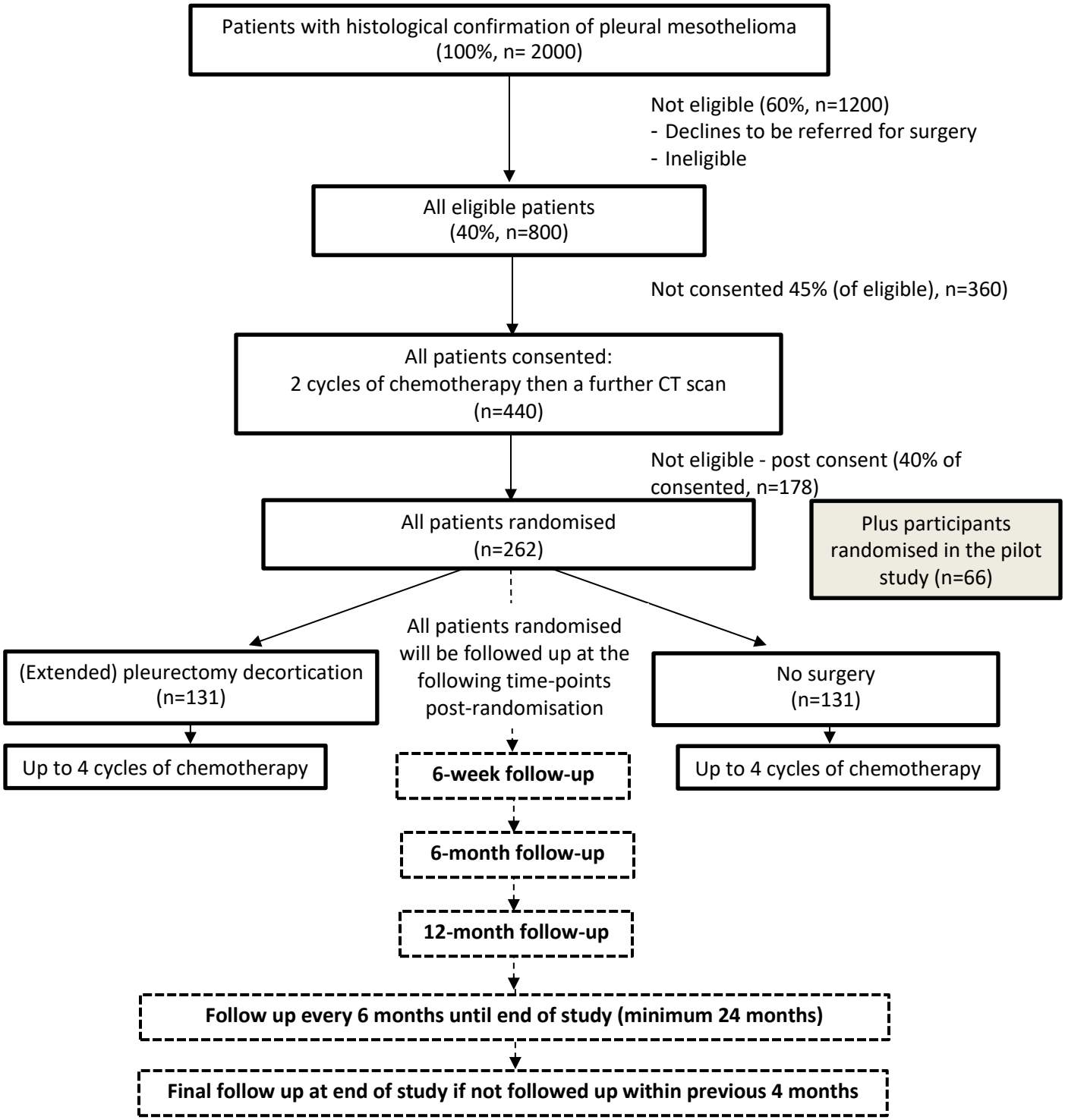
Specific objectives are to estimate:

A. The difference between groups in terms of overall survival.
B. The difference between groups with respect to a range of secondary outcomes including health related quality of life (HRQoL), progression free survival and measures of safety (adverse health events).
C. The cost effectiveness of (extended) pleurectomy decortication compared to no (extended) pleurectomy decortication.

5. Plan of Investigation

5.1 Trial schema

Figure 1 Trial schema



5.2 Trial design

MARS 2 is a multi-centre, open parallel two-group, pragmatic randomised controlled trial (RCT) of chemotherapy alone or chemotherapy and surgery for suitable patients with mesothelioma.

The pilot trial demonstrated feasibility of recruitment in 14 medical centres and 2 joint medical and surgical centres of excellence. For the full trial further medical and joint medical and surgical centres will be opened and recruiting centres will be supported with an integrated QuinteT Recruitment Intervention (QRI). A study manual and measures of surgical quality standards, with assessment and confirmation of fidelity for all new participating surgical centres, will be developed.

Patients will be followed up for quality of life and resource use outcomes 6 weeks post randomisation and then every six months over a two-year period. After this, patients will be followed up for disease progression, further treatment and survival every six months to the end of the trial (up to 60 months post randomisation).

5.3 Setting, centre and surgeon eligibility

This study will take place in NHS secondary care centres, including teaching and district general hospitals.

To be eligible as a medical site, the centre must

i) be a NHS Trust with access to a multidisciplinary team (MDT) to discuss patients with mesothelioma
ii) have a track record of treating patients with mesothelioma. Participants from all medical (only) sites are referred to a trial-accredited surgical site for CT assessment of eligibility and surgery (if randomised to surgery).

To be eligible as a surgical site, the centre must

i) be a NHS Trust with an established mesothelioma MDT
ii) have a minimum of 2 named mesothelioma surgeons participating in the trial.

In the pilot study surgeons were required to have a track record of undertaking (extended) pleurectomy decortications as reported to the Society for Cardiothoracic Surgery. In this main trial, newly participating surgeons must

i) be accredited by observing the procedure undertaken at an established site
ii) have an established first-wave surgeon observe the first procedure undertaken, and
iii) have one randomly selected operation between procedure 5 to 10 observed by an established first-wave surgeon to ensure fidelity.

5.4 Key design features to minimise bias

(a) Bias arising from the randomisation process (systematic differences between baseline characteristics of the groups that are compared) will be prevented by concealed randomisation (see section 6.1).

(b) Bias due to deviations from intended interventions (systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest) will be minimised by defining the intervention and comparator, as well as standard protocols for other procedures undertaken during the trial (see section 5.6); pre-defining all procedures for participant follow-up and applying the procedures to all participants in the same way (see section 6.11). Adherence to all aspects of the protocol will be monitored (for further details see section 8.2 and 8.3)

(c) Bias in measurement of the outcome (systematic differences between groups in how outcomes are determined) will be minimised by using an objective primary outcome measure (survival) (see section 6.6); and also by providing clear unambiguous definitions for each of the secondary outcome measures (see section 5.7).

(d) Bias due to missing outcome data (systematic differences between groups in withdrawals from a study) will be minimised by: using established Bristol Trials Centre (BTC) Clinical Trials and Evaluation Unit (CTEU) methods to maximise the proportion of participants for whom all outcome data are available (see section 6.12); documenting non-adherence to random allocations (see section 7.1); using intention to treat analysis and investigating sensitivity to attrition bias in statistical analysis (see section 7.1); investigating sensitivity to attrition bias in the statistical analysis, implementing appropriate imputations for missing data (see section 7.1).

(e) Bias in selection of the reported results will be minimised by having pre-specified outcomes (see section 4.6) and a pre-specified analysis plan (see section 6.0).

5.5 Trial population

The target population are patients with tissue confirmed mesothelioma confined to one hemi-thorax and deemed (by a MARS 2 surgeon) to be potentially surgically resectable.

5.5.1 Inclusion criteria

Patient may enter study if ALL of the following apply

1. 16 years of age or over
2. Tissue (cytology or histology) confirmed epithelioid, sarcomatoid or biphasic mesothelioma*
3. Disease confined to one hemi-thorax based on CT assessment
4. Disease deemed surgically resectable**
5. Fit for surgery**
6. Capacity to provide written informed consent to participate in the trial

*The “diagnosis” of mesothelioma is based on cytology and / or histopathology results as reviewed by MDT to be of sufficient certainty to recommend chemotherapy as treatment.
**To be confirmed by a surgeon at a MARS 2 surgical site

5.5.2 Exclusion criteria

Patient may not enter study if ANY of the following apply

1. Severe shortness of breath (this is defined as an Eastern Cooperative Oncology Group (ECOG) status ≥ 2, or if lung function tests are performed: pre-operative forced expiratory volume after one second (FEV_1) or transfer factor of the lung for carbon monoxide (TLco) less than 20%);
2. Serious concomitant disorder that would compromise participant safety during surgery (e.g. evidence of end organ failure)
3. Severe heart failure (this is defined as NYHA III or IV or if an echocardiogram is performed an ejection fraction less than 30%)
4. End stage kidney failure requiring dialysis
5. Liver failure (e.g. encephalopathy and/or coagulation abnormalities)
6. Prisoner
7. Patient lacks capacity to consent
8. Existing co-enrolment in another interventional clinical trial that aims to improve survival

5.6 Trial interventions

5.6.1 Experimental group

The experimental intervention is chemotherapy and surgery for mesothelioma.

Pleurectomy decortication surgery involves removal of the lining of the chest wall and lining of the lung, possibly also with the sac around the heart and / or diaphragm (“extended”) as required to achieve complete tumour removal but leaving the lung in-situ. The definition of the procedure is in accordance with international consensus stipulated by a working group under the auspices of the International Association of The Study of Lung Cancer. (11)

The decision to perform pleurectomy decortication or extended pleurectomy decortication will be made by the surgeon based on surgical findings.

Participants will receive 2 cycles of platinum and pemetrexed chemotherapy followed by surgery and then up to 4 cycles of platinum and pemetrexed chemotherapy.

5.6.2 Control group

The control intervention is up to 6 cycles of platinum and pemetrexed chemotherapy alone (current standard of care).

5.6.3 Chemotherapy and additional therapies

After randomisation, for patients with progressive disease, any changes in the choice of chemotherapy or addition of other agents or entry into therapeutic trials (e.g. immunotherapies) will not be restricted, but will be documented. The aim is to conduct a pragmatic trial, but uptake of additional therapies and trials will be closely monitored.

Whilst an active participant in the trial, patients in both arms can receive further surgery (as long as it is without radical intent, e.g. talc pleurodesis, indwelling pleural catheters, repeat biopsies).

As there is no current national consensus on post-operative prophylactic radiotherapy, irradiation to thoracic procedure sites may be undertaken as stipulated in local practice guidelines. Details of any radiotherapy given are to be documented on the case report form (CRF).

5.7 Primary and secondary outcomes

5.7.1 Primary outcome

The primary outcome is survival. This has been chosen because the aim of radical surgery is to improve the length of life in patients with mesothelioma, a disease with a very poor prognosis.

5.7.2 Secondary outcomes

Secondary outcomes have been selected to assess the efficacy of the two approaches and include:

- Progression free survival to the end of the trial (minimum of two years after randomisation)
- Serious adverse health events to the end of the trial
- HRQoL: EORTC QLQ-C30, and EQ-5D-5L to two years (measured at 6 weeks, 6, 12, 18 and 24 months after randomisation)
- Resource and health service use to two years (measured at 6 weeks, 6, 12, 18 and 24 months after randomisation) and during initial surgical admission for surgical arm.

5.8 Sample size

The study hypothesis is that the overall survival for patients undergoing (extended) pleurectomy decortication will improve by 30% (hazard ratio 0.70). The baseline survival of patients eligible for surgery but only receiving medical treatment was obtained from the estimate by Utley et al as 16.8 months.(12)

The relative difference of 30% was regarded as the minimally important difference for patients and clinicians to choose surgery given the risks of the procedure. The figure was chosen by the trial's patient and public involvement (PPI) group and agreed by the trial management group (TMG) during the study design phase in 2011. The possibility that survival could be worse with surgery was also discussed, and a relative difference of 30% also regarded as an appropriate difference to indicate harm, therefore a two-tailed test for superiority was agreed.

The total sample size has been set at 328 participants (164 per group). The study will have 80% power to detect a hazard ratio of 0.7 at 5% statistical significance (2-sided), assuming a median survival of time 16.8 months in the no surgery group and allowing for 10% cross-over from the medical to surgery groups (as noted in previous trials such as MARS 1). Cross-over will be minimised through instruction (i.e. recruit only patients who have equipoise from the outset) and education (i.e. QRI).

The pilot trial (using the same intervention protocol) recruited over a 2-year period and randomised 66 patients by June 2017. These participants will contribute to the total sample size, so the target recruitment for the full trial is 328 – 66 = 262 participants.

6. Trial methods

6.1 Description of randomisation

Randomisation will be carried out electronically using a secure web-based system (Sealed Envelope (https://sealedenvelope.com). The allocation will not be revealed until sufficient information to uniquely identify the participant has been entered.

Minimisation (with a random component) for selected baseline variables (age, performance status and cell type) that influence survival, in addition to stratification by centre to ensure that the cohorts are as balanced as possible, will be applied. Randomisation will be carried out by a member of the research team at the medical centre after the participant has received 2 cycles of chemotherapy, and had a further CT scan to confirm eligibility (i.e. resectable disease). Participants will also have completed a second set of HRQoL questionnaires prior to randomisation.

6.2 Blinding

Participants and clinical personnel will not be blinded to allocation and the trial will be at risk of measurement of outcome bias. The patient information leaflet (PIL) and the process of obtaining informed consent will describe the potential effects of surgery. Therefore, the participant should not have a strong expectation that one or other method should lead to a more favourable result.

6.3 Research procedures

6.3.1 Pre randomisation research assessments

Eligible consented patients will undergo an initial two cycles of standard of care chemotherapy (e.g. platinum and pemetrexed; ~3 weeks per cycle) followed by a repeat CT to assess progression beyond one hemi-thorax (occurs in approximately 10%). A contrast and pleural enhancement protocol is recommended to screen for progressive disease as per the RECIST criteria.(13) Progression beyond surgically resectable limits must, again, be assessed by a surgeon at a MARS 2 surgical site.

It is recommended that the CT scan is performed towards the end of the 2nd week of the second cycle of chemotherapy to avoid delays in treatment. If there is no evidence of progression beyond surgically resectable limits, participants will be randomised into the trial. In the rare instances where a patient's

disease has progressed, but not beyond surgically resectable limits, then this will be documented, but the patient will still be randomised.

Participants will undergo a lung function test at baseline (i.e. after consent), if this has not already been performed prior to screening. They will also be asked to complete HRQoL questionnaires at baseline and again after completion of the 2 cycles of chemotherapy and before randomisation.

6.3.2 Post randomisation research assessments

All participants will be followed at 6 weeks, 6, 12, 18 and 24 months post randomisation, and following this, every 6 months until the end of the trial, and again at the end of the trial if not within the previous 4 months. Participants receiving surgery will also be followed postoperatively to discharge.

Up until 24 months, participants will be followed up by telephone (local research team will contact patients at mutually agreed times, unless patients will be attending hospital anyway, in which case face to face follow up can be completed) to ascertain serious adverse events, health service and resource use. HRQoL questionnaires will be completed by post or online according to the participant's preference. Reminders will be sent by post, email and/or SMS as appropriate. If participants fail to respond they may be contacted by the local research team and invited to complete the questionnaires by telephone. After 24 months, participants will continue to be followed up by postal questionnaire to ascertain any additional treatment received, recurrence or new cancer and participation in any other trials. If participants fail to respond they may be contacted by the local research team and invited to complete the questionnaires by telephone.

6.3.3 The QuinteT Recruitment Intervention (QRI)

Recruitment to RCTs can be challenging (14), particularly for surgical trials (15). Research has consistently shown that the success of an RCT is dependent on employing effective and efficient methods for recruiting participants (16, 17). In line with this, a QRI can be integrated into RCTs to optimise recruitment and informed consent. These methods used were developed initially in the ProtecT (Prostate testing for cancer and Treatment) study (18, 19), and have subsequently been used and further refined in in over 25 RCTs.(20)

The aim of the QRI is to understand the recruitment process and how it operates in clinical centres, so that sources of recruitment difficulties can be identified and suggestions made to change aspects of design, conduct, organisation or training that could then lead on to improvements in recruitment. The QRI will be undertaken in two stages:

Phase I: Understanding recruitment

Phase I aims to understand the recruitment process and how it operates in clinical centres. A multi-faceted, flexible approach will be used to investigate site-specific or wider recruitment obstacles. These will comprise the following:

a) In-depth interviews: Semi-structured interviews will be undertaken with three groups: i) members of the TMG, ii) clinicians or researchers who are involved in trial recruitment, iii) eligible patients who have been approached to take part in the trial, and iv) PPI group members. Interviews with members of the

TMG and recruiters will explore their perspectives on MARS 2, and where relevant, their experiences of recruitment. Key topics explored will include perspectives on the trial design and protocol; views about the evidence on which the trial is based; perceptions of uncertainty/equipoise in relation to the RCT groups; views about how the groups/protocol are delivered in their clinical centre; methods for identifying eligible patients; views on eligibility, and examples of actual recruitment successes and difficulties. Interviews with patients will explore views on the presentation of study information, understandings of trial processes (e.g. randomisation), and reasons underlying decisions to accept or decline the trial. Patients will be purposefully sampled, to build a sample of maximum variation on the basis of age, sex, study centre, and the final decision about trial participation (i.e. accept or decline randomisation).

b) Analysis of audio-recorded recruitment discussions: Scheduled appointments during which the trial is discussed will be audio-recorded with permission, including telephone conversations. The audio recordings will be used to explore information provision, recruitment techniques, management of patient treatment preferences, and randomisation decisions to identify recruitment difficulties and improve information provision.

c) Mapping of eligibility and recruitment pathways: Detailed eligibility and recruitment pathways will be compiled for clinical centres, noting the point at which patients receive information about the trial, which members of the clinical team they meet, and the timing and frequency of appointments. Recruitment pathways will be compared with details specified in the trial protocol and pathways from other centres to identify practices that are potentially more/less efficient. The QRI researcher will also work closely with the BTC (CTEU) to compose detailed logs of potential participants as they proceed through screening and eligibility phases, to help identify points at which patients do not continue with recruitment to MARS 2. Logs of eligible and recruited patients will be assembled using simple flow charts and counts to display numbers and percentages of patients at each stage of the eligibility and recruitment processes. These figures will be compared across centres and considered in relation to estimates specified in the grant application/study protocol.

d) Observation of TMG and investigator meetings: The QRI researcher will regularly observe TMG meetings to gain an overview of trial conduct and overarching challenges (logistical issues, etc.). Observation of these meetings can elucidate new lines of enquiry and add new dimensions to challenges that have emerged through other data collection methods.

Phase II: Feedback to CI/TMG and implementing strategies to optimise recruitment

The QRI research team will present summaries of anonymised findings to the Chief Investigator (CI) and TMG, identifying the factors that appear to be hindering recruitment with supporting evidence. The QRI team will then suggest a potential plan of action to improve recruitment, based on the findings from Phase I but also including experience from other RCTs for generic issues. The CI/TMG will then need to decide on the content of their plan of action to improve accrual in any low recruiting centres.

The aspects that the QRI team will be able to work with the RCT team on are likely to include providing feedback and training on generic recruitment issues, such as how to present MARS 2's design more clearly to improve levels of understanding during informed consent, how to approach patients' treatment preferences, and, perhaps, facilitating discussions around issues of eligibility assessment, equipoise, and team-working, or potential changes to the protocol – as appropriate. The responsibility

for deciding on the details of the plan of action and implementing changes and facilitating the QRI team's work will lie with the CI.

6.3.4 Central Pathology Review

For pathology QA purposes, the slides of 10% of all cases will be reviewed by an independent pathologist to confirm histological sub-diagnosis. All histology samples that are deemed as: 'Unable to classify' at baseline or post-operatively, and where the histological sub-diagnosis varies pre- and post-operatively, will also be reviewed by the independent pathologist to confirm sub-diagnosis. The slides will be pseudonymised before being sent to the independent pathologist for review.

BTC (CTEU) will be responsible for requesting the relevant slides and pathology reports from each site. BTC (CTEU) will organise transfer of slides via 'Safe Boxes' using Special Delivery. If a MARS 2 site team can provide digital images of the slides, these will be emailed to the MARS 2 nhs.net secure email address. BTC (CTEU) will thereafter send the pseudonymised samples and reports to the Pathology Department at Royal Brompton & Harefield NHS Foundation Trust for review. Once the histology slides have been assessed they will either be securely disposed of (if appropriate) or returned to the BTC (CTEU) team for distribution back to the relevant MARS 2 site team.

6.4 Duration of treatment period

All consented patients will undergo an initial two cycles of standard of care chemotherapy (e.g. platinum and pemetrexed; ~3 weeks per cycle)

6.4.1 Patients randomised to Surgery

Patients will be admitted for surgery. Patients are usually in hospital for approximately 10-14 days for this type of procedure and post-operative recovery is usually estimated to be 3 weeks.

Patients will be given 4 further cycles of chemotherapy (platinum and pemetrexed) (~3 weeks per cycle) as standard of care. It is recommended these next four cycles of chemotherapy are commenced within 12 weeks of the operation to avoid delays in treatment.

6.4.2 Patients randomised to No Surgery

Patients will receive up to a further 4 cycles of chemotherapy (platinum and pemetrexed) as standard of care (~3 weeks per cycle).

6.5 Definition of end of trial

When all patient follow up has been completed (2 years after the last participant is randomised), all data entry has been completed, all data queries cleared and the database has been locked and analyses completed.

The end of trial for the participant is when they have completed all follow up visits/questionnaires or they have withdrawn from the study.

6.6 Data collection

Data collection will include the following elements:

(a) A log of patients with a confirmed diagnosis of malignant pleural mesothelioma and those who are approached about the trial (including the date when they are given the PIL).

(b) Patients approached and assessed against the eligibility criteria and, if ineligible, reasons for ineligibility.

(c) Consent (and reasons for declining trial entry) and baseline information (e.g. demographics, medical history, lung function tests - if not done prior to screening as part of routine care, blood test results and response to HRQoL questionnaires) collected prior to first 2 cycles of chemotherapy.

(d) Chemotherapy treatment given (initial 2 cycles, and up to 4 further cycles post-randomisation)

(e) Result of post-chemotherapy (initial 2 cycles) CT scan to assess eligibility for randomisation

(f) Response to HRQoL questionnaires (pre-randomisation; and at 6 weeks and 6, 12, 18 and 24 months post-randomisation)

(g) In hospital operative and post-operative data (surgery group)

(h) Adverse events from time of consent to the end of the trial (2 years after the last participant is randomised).

(i) Resource and health service use from time of consent to the end of the trial (2 years after the last participant is randomised).

Resource use data will be collected for all participants on chemotherapy cycles and surgery (if applicable, this will include details of the surgical procedure, length of stay in hospital by level of care, and post-operative complications) by adding questions to the trial CRFs. Further resource use data will be captured from participants at each of the follow up telephone calls.

To minimise bias, outcome measures are defined as far as possible on the basis of objective criteria.

Table 1 Data collection

Data item	*Screening*	*Baseline*	*2 cycles chemotherapy*	*Randomisation*	*Surgery**	*Up to 4 cycles chemotherapy*	*Post randomisation*					
							6 w	*6 m*	*12 m*	*18 m*	*24 m*	*Every 6 m and end of trial***
Screening log	✓			✓								
CT scan	✓***			✓								
Informed consent		✓										
Demography, medical history, blood test results		✓										
Lung function tests	✓	✓****										
HRQoL		✓		✓			✓	✓	✓	✓	✓	
*Chemotherapy treatment given****			✓			✓						
*Surgery and in hospital post-operative data*****					✓							
Adverse events					✓		✓	✓	✓	✓	✓	✓
Patient reported resource and health service use							✓	✓	✓	✓	✓	
Disease progression, further treatments, survival												✓

* Patients allocated to surgery and/or receiving surgery only

** If not within previous 4 months

*** Previous CT scan to be used (not to be done again specifically for the trial protocol)

**** Only one assessment of lung function is needed so if this has been done prior to screening there is no need for another test at baseline

***** Including resource and health service use

6.7 Source data

Source data will be the patient's medical records and patient-reported questionnaires and where information is not recorded anywhere else, the case report forms (CRFs) are the source data.

6.8 Planned recruitment rate

The aim is to randomise 22 patients per quarter over three years, a figure that is felt to be achievable given the results of the pilot trial. Recruitment will be further optimised in current high-volume but low-recruitment sites through the QRI (see section 6.3.3) and opening further medical and surgical centres. With regards to new surgical sites, priority will be given to geographic representation for Scotland and London, as the two current surgery centres are in the Midlands, in order to reduce travelling distance and facilitate trial recruitment.

6.9 Participant recruitment

At the earliest opportunity in the patient pathway, potential participants will be given a PIL (approved by the Research Ethics Committee (REC)) describing the study. The patient will be asked if they give permission for their most recent CT scan (it is recommended that the most recent CT scan is within the past 4 weeks) to be referred to a surgeon at one of the MARS 2 surgical centres. If the patient's disease is potentially resectable they will be invited to attend an out-patient appointment at the surgical centre. If their disease is considered inoperable they will receive standard medical care.

The patient will have time to read the PIL and to discuss their participation with others outside the research team (e.g. relatives or friends) if they wish.

If the patient's disease is potentially resectable and if they meet the eligibility criteria, the surgeon (or delegated member of the study team at the surgical centre) will discuss the study in more detail with the patient and, if required, give the patient another copy of the PIL.

The surgical centre will advise the referring medical centre that the patient may be eligible for randomisation. The patient will then be invited back to the MARS 2 medical centre to discuss the study. Patients will be seen by a member of the local research team (study clinician/research nurse/trial coordinator) who will answer any questions, confirm the patient's eligibility and take written informed consent if the patient decides to participate.

If the patient consents to audio-recording of consultations (QRI component), all discussions about trial participation will be audio-recorded until the patient has reached a decision. It is beneficial if as many consultations during the patient pathway as possible can be audio-recorded, therefore consent to audio-recording will be requested at the earliest possible opportunity. This may be verbal consent in the first instance, with a view to obtaining written informed consent subsequently. This will be on the understanding that the data will not be uploaded/submitted or used until written consent has been obtained.

As part of the QRI component of the study, patients may also be asked if they would like to take part in an interview with one of the study qualitative researchers. Patients will be asked if they agree to be contacted by a qualitative researcher when they consent to the audio-recording. Patients who do not

consent to audio-recording, may agree verbally to be contacted about an interview (and this will be documented on the study CRFs). One of the study qualitative researchers will contact the patient to explain more about the interview and, where patients have not given written consent (i.e. signed an 'interview' consent form) but want to proceed with an interview over the phone, the researcher will capture their verbal consent for the interview to go ahead. A consent form will then be posted for the patient to complete and return, and data from the interview will not be used until written consent has been received. Where relatives/carers are present and wish to participate in the patient interview, verbal consent for their data to be used will be sought.

Details of all patients approached for the trial and reason(s) for non-participation (e.g. reason for being ineligible or patient refusal) will be documented. During the consent procedure, it will be explained to the patient that they may not be randomised into the study if their disease has progressed as assessed by CT scan after 2 cycles of standard of care chemotherapy (platinum and pemetrexed) to beyond the limits of surgical resection. Participants' General Practitioners will be informed of their enrolment in the study.

After 2 cycles of chemotherapy a CT scan will be performed and assessed by the MARS 2 surgical centre that will be performing the surgery (or another MARS 2 surgeon or the CI, if the surgeon(s) at the relevant surgical centre are not available). It is recommended that the CT scan should be reviewed within one week to ensure the chemotherapy regimen is not delayed in those patients randomised to no surgery.

The surgical centre/CI will advise the medical centre if a patient's disease has not progressed beyond surgically resectable limits and therefore that the patient is eligible for randomisation.

Patients whose disease has progressed and is not deemed surgically resectable (and are therefore not randomised) will receive standard medical care and will not continue in the study.

6.10 Discontinuation/withdrawal of participants

Each participant has the right to withdraw at any time. In addition, the investigator may withdraw the participant from their allocated treatment arm if subsequent to randomisation a clinical reason for not performing the surgical intervention is discovered. If this occurs this will be appropriately documented.

If a participant wishes to withdraw, we will continue to analyse any data already collected, unless the participant expresses a wish for their data not to be included.

6.11 Frequency and duration of follow up

Follow up dates will be defined from the date of randomisation. Patients will be followed up at 6 weeks, and 6, 12, 18 and 24 months, and then every 6 months until the end of the study, and again at the end if not within the previous 4 months.

Patients who have had surgery will attend the surgical centre for the post-operative check (usually at 3-6 weeks post-surgery).

6.12 Likely rate of loss to follow-up

There are no special features to minimise attrition bias. Established BTC (CTEU) methods will be used to maximise the proportion of participants for whom all outcome data are available and the proportion of participants who receive the intervention to which they were allocated.

6.13 Expenses

Travel expenses are offered for pre-surgical, surgery and post-operative consultation visits to the surgical centre that are in addition to routine care.

7. Statistical analyses

7.1 Plan of analysis

The data will be analysed according to intention to treat (ITT) and follow CONSORT reporting guidelines. Analyses will be adjusted for centre and for design factors included in the cohort minimisation (e.g. age, performance status and cell type).

Survival time and progression free survival time will be compared using survival methods, allowing for censoring of any participant who is either alive or lost to follow-up at the end of the follow-up period. HRQoL will be compared using a mixed regression model, adjusted for baseline measures where appropriate. Changes in treatment effect with time will be assessed by adding a treatment x time interaction to the model and comparing models using a likelihood ratio test. Deaths will be accounted for by modelling HRQoL and survival jointly. Model fit will be assessed and alternative models and/or transformations (e.g. to induce normality) will be explored where appropriate. Treatment differences will be reported with 95% CIs. A sensitivity analysis investigating the effect of surgeon (surgical group only) will be performed for the primary outcome.

Frequencies of adverse events will be described, and the numbers of participants experiencing one or more SAEs during the follow-up period will be compared. A detailed analysis plan will be prepared. Interim analyses will be decided in discussion with the Data Monitoring and Safety Committee (DMSC).

Reasons for non-completion of any assessment will be recorded and coded. Missing items or errors on questionnaire measures will be dealt with according to the scoring manuals or via imputation methods. Compliance rates will be reported in results, including the numbers of patients who have withdrawn from the study, have been lost to follow up or died. Causes of death for trial participants will be recorded, but copies of death certificates will not be sought.

7.2 QRI data analyses

Interviews and recruitment consultations will be audio-recorded, fully transcribed and, along with recruitment screening logs and observations, subject to simple counts, content, thematic and targeted conversation analyses. Preliminary analysis will be used to inform training and further data collection. Members of the qualitative team will independently analyse a proportion of transcripts to assess the dependability of coding and will meet regularly to review coding and descriptive findings, agree further

sampling and training strategies, and discuss theoretical development – all in close collaboration with the CI.

7.3 Subgroup analyses

Two subgroup analyses are planned: i) comparing primary and secondary outcomes by the experience level of the surgical centre; and ii) comparing the primary outcome by type of mesothelioma (epithelioid, sarcomatoid or biphasic).

7.4 Frequency of analyses

The primary analysis will take place when follow-up is complete for all recruited participants. Safety data will be reported to the DMSC at a frequency to be agreed, together with any additional analyses the committee requests. In these reports the data will be presented by group but the allocation will remain masked, where possible.

7.5 Criteria for the termination of the trial

The trial may be stopped early on the advice of the DMSC or if the results of another study supersede the necessity for completion of this study.

7.6 Economic Evaluation

The economic evaluation will compare the costs and effects of (extended) pleurectomy decortication versus no (extended) pleurectomy decortication for the treatment of pleural mesothelioma, and will follow established guidelines as set out by the National Institute for Health and Care Excellence (NICE).(21) The within-trial cost-effectiveness analysis will be undertaken from an NHS and personal social services perspective, with a time horizon from time of consent to 24 months post-randomisation. The primary outcome measure for the economic evaluation will be quality adjusted life years (QALYs), estimated using the EuroQol EQ-5D-5L,(22, 23).

Unit costs will be derived from nationally published sources and Trust finances and attached to the resource use data.

Missing data will be handled using multiple imputation methods.(24) From the average costs and QALYs gained in each trial group, the incremental cost-effectiveness ratio will be derived, producing an incremental cost per QALY gained of (extended) pleurectomy decortication compared to no surgery.(25) (Extended) pleurectomy decortication will be considered cost-effective if the incremental cost-effectiveness ratio falls below £20,000, the level below which NICE generally recommends interventions to the NHS.(26) Univariate and multivariate sensitivity analyses will show what impact varying key parameters in the analysis has on baseline cost-effectiveness results. Results will be expressed in terms of a cost-effectiveness acceptability curve, which indicates the likelihood that (extended) pleurectomy decortication is cost-effective for different levels of willingness to pay for health gain.

8. Trial management

8.1 Trial Oversight

The trial will be managed by a TMG, which will meet face-to-face or by teleconference as agreed with the CI. The TMG will be chaired by the CI and will include members of the named research team as required (see *Chief Investigators & Research Team Contact Details)*.

The TMG will be supported by BTC (CTEU) which is a UK Clinical Research Collaboration registered Clinical Trials Unit. BTC (CTEU) will prepare all the trial documentation and data collection forms, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the clinical investigators.

8.2 Day-to-day management

An appropriately qualified person by training will be responsible for identifying potential trial participants, seeking informed participant consent, randomising participants, collecting trial data and ensuring the trial protocol is adhered to.

8.3 Monitoring of sites

8.3.1 Site Initiation

Before this protocol is implemented training session(s) will be organised by BTC (CTEU). These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the study.

8.3.2 Site monitoring

The trial coordinating centre will carry out regular monitoring and audit of compliance of centres with GCP and data collection procedures described in section 5.5.

8.4 Trial Steering Committee and Data Monitoring and Safety Committee

Trial Steering Committee
The TSC will have an independent Chair and independent members covering specialities such as thoracic surgery, oncology and radiology. There will also be an independent statistician and heath economist as well as a PPI representative. The Terms of Reference will be agreed by the committee.

Data Monitoring and Safety Committee
The DMSC will have an independent statistician as Chair along with a thoracic surgeon and oncologist covering specialist such as thoracic surgery, medical statistics, oncology and radiology. The DMSC for the MARS 2 pilot have developed a charter outlining their responsibilities and operational details.

9. Safety reporting

Serious adverse events will be recorded and reported in accordance with Good Clinical Practice (GCP) guidelines. In thoracic surgery, post-operative transient complications are not unexpected and are not infrequent. Unexpected events are those not listed in the trial protocol or on the CRFs (E2/D5). The procedure for safety reporting is shown below (Figure 2).

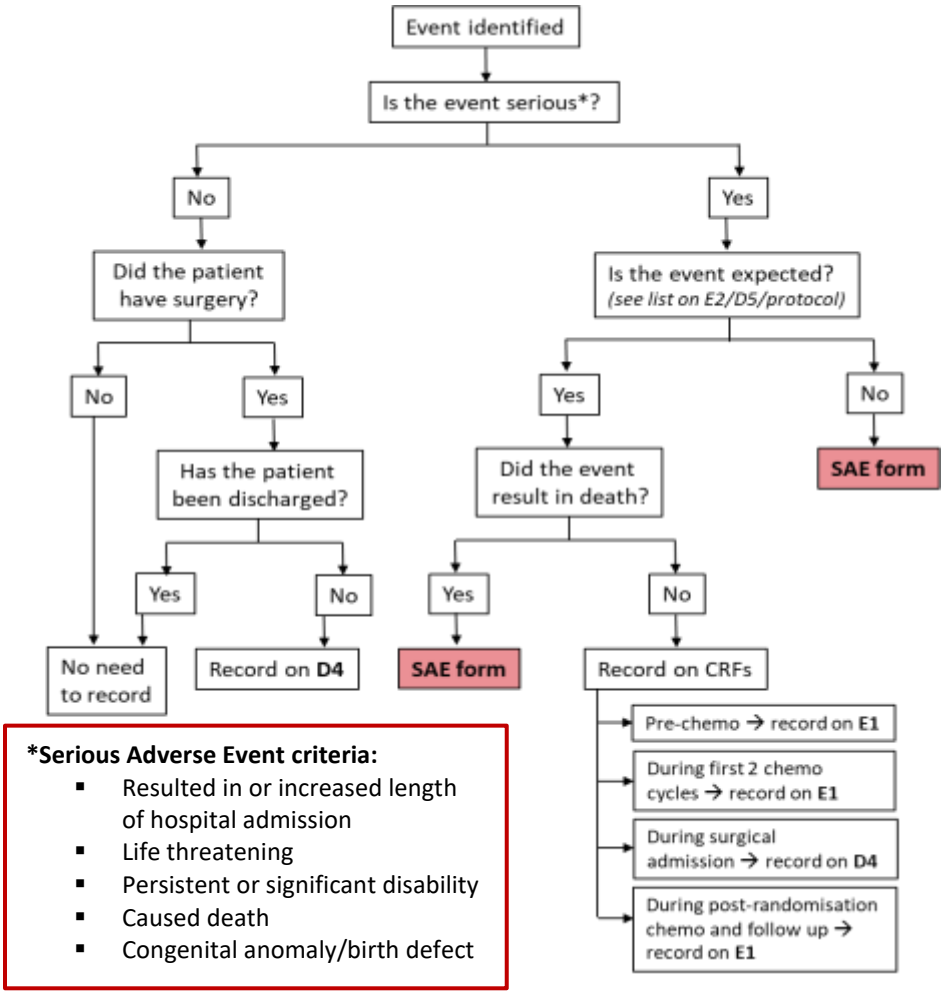


Figure 2 Serious adverse event reporting flow chart

All 'unexpected' SAEs related to the intervention and any fatal SAEs should be reported to the co-ordinating centre via scanned copies of the SAE forms (S1 and S2) within 24 hours of the local site staff becoming aware of the event, even if sections of the forms are incomplete**.** Related events are those judge possibly, probably or definitely related to the trial intervention (surgery). Scanned copies of the SAE forms should be emailed to the co-ordinating centre (mars2-trial@bristol.ac.uk).

All other 'unexpected' SAEs should be entered on to the MARS 2 database via the SAE forms (S1 and S2) as soon as possible.

For SAE events that have been deemed as 'ongoing', the co-ordinating centre should be updated when new information becomes available about the event. Updated information can be provided by scanned copies of the S3 form and emailed to mars2-trial@bristol.ac.uk or entered directly on to the S3 form in the MARS 2 database.

The co-ordinating centre will report all 'unexpected' and 'related' SAEs to the REC, DMSC and local PIs within 15 days of becoming aware of the event and copy all reports to the Trial Sponsor.

The co-ordinating centre will report all post-operative deaths (those occurring during the hospital admission for surgery and up to 30 days post-surgery) to the DMSC within 7 days of becoming aware of the event and copy all reports to the Trial Sponsor.

The DMSC will review all SAEs at their regular meetings.

Note: Elective surgery and treatment during the follow-up period that was planned prior to recruitment to the trial will not be reported as an unexpected SAE.

9.1 Expected adverse events

The following adverse events are expected and would not require a separate SAE form unless the event results in death. Expected adverse events are recorded as shown in Figure 2

9.1.1 Adverse events considered as 'expected' for patients undergoing this type of surgery

Expected morbidity following this type of thoracic surgery can include:

Procedural complications:

Pulmonary:
- Atelectasis/ Pulmonary collapse
- Pneumonia / Chest Infection (defined by the administration of antibiotics)
- Empyema (defined as the requirement for antibiotics or drainage)
- Bronchopleural fistula
- Prolonged air leak (defined as ≥ 7 days) or other post-drain pneumothorax requiring intervention
- Chylothorax
- ARDS (acute onset of respiratory failure, bilateral infiltrates on chest radiograph, hypoxemia as defined by a PaO2/FiO2 ratio ≤200 mmHg, and no evidence of left atrial hypertension or a pulmonary capillary pressure <18 mmHg (if measured) to rule out cardiogenic oedema).
- Acute Lung Injury (ALI), defined as above but by a 200 < PaO2/FiO2 ≤300 mmHg)
- Open & close thoracotomy in the event of inoperable cancer or extensive malignancy
- Bronchoscopy for any cause

Thromboembolic complications*:*
- Deep vein thrombosis
- Pulmonary embolus

Renal complications*:*

- New haemofiltration/dialysis

***Infective complications**:*
- Sepsis (defined as antibiotic treatment for suspected infection)
- Wound infection
- Respiratory infection

***Neurological complications**:*
- Transient ischaemic attack
- Stroke
- Laryngeal nerve damage

Cardiovascular:
- Bleeding
- Haematoma
- Venous thromboembolism (VTE)
- Myocardial infarction (MI)
- Atrial Fibrillation

Gastrointestinal:
- Peptic ulcer/GI bleed/perforation
- Pancreatitis (amylase >1500iu)
- Other (e.g. laparotomy, obstruction)

Other:
- Re-operation for any reason (other than recurrence or progression)
- Wound dehiscence requiring treatment
- Pain
- Patch disruption
- Abdominal organ herniation into the chest

As with all major surgery there is also a risk of death. The risk of in-hospital death with pleurectomy decortication is three per hundred.(27)

All post-operative deaths (those occurring during the hospital admission for surgery and up to 30 days post-surgery) will be reviewed by the DMSC within 7 days of the event being reported to the co-ordinating centre.

9.1.2 Adverse events considered as 'expected' for patients undergoing chemotherapy

The following adverse events are considered expected. Additional adverse events may also be considered expected if identified on the product summary of product characteristics (SPC) of the chemotherapy treatments used.

Blood & lymphatic complications:
- Anaemia
- Thrombocytopenia

- Neutropenia (Febrile Neutropenia)
- Myelosuppression

Gastrointestinal complications:
- Nausea
- Vomiting
- Diarrhoea
- Constipation

Infectious complications:
- Infections

Nervous system complications:
- Peripheral sensory neuropathy
- Peripheral motor neuropathy
- Headaches
- Insomnia

Immune system complications:
- Anaphylaxis / Hypersensitivity reaction
- Muscular complications
- Arthralgia
- Myalgia

Abnormal laboratory results:
- Leukopenia
- Elevated AST / ALTs
- Elevated alkaline phosphatase

9.1.3 Adverse events considered as 'expected' for patients with the condition:

- Disease recurrence includes local, regional and distant recurrence
- New primary and secondary cancers
- Disease progression
- Death from disease progression*

*All fatal SAEs, whether expected or unexpected should be reported to the co-ordinating centre within 24 hours of becoming aware of the event, as detailed above.

9.2 Period for recording serious adverse events

Data on serious adverse events will be collected from date of consent for the duration of the participant's post-operative hospital stay and for the entire follow-up period.

10. Ethical considerations

10.1 Review by an NHS Research Ethics Committee

Ethics review of the protocol for the trial and other trial related essential documents (e.g. PIL and consent form) will be carried out by a UK REC.

Any amendments to these documents, after a favourable opinion from the REC has been given, will be submitted to the REC and HRA for approval prior to implementation. Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving REC/HRA approval. However, in this case, approval must be obtained as soon as possible after implementation.

10.2 Risks and anticipated benefits

There should be no additional risk to participants when taking part in this study as neither (extended) pleurectomy decortication nor no (extended) pleurectomy decortication are new or experimental. However, at present there is a lack of well-designed empirical evidence to suggest that one technique is superior to the other; this forms the rationale for this study and will be the main benefit to society. Such evidence will inform NHS policy and patient and clinician decision-making.

10.3 Informing potential study participants of possible benefits and known risks

It will be explained to the patient that they may not necessarily benefit individually by participating in the trial but the knowledge gained will be used to help define the optimum care of Mesothelioma patients in the future.

10.4 Obtaining informed consent from participants

All participants will be required to give written informed consent. This process, including the information about the trial given to patients in advance of recruitment, is described above in section 6.9.

The research nurse/trial coordinator/PI/clinical research fellow/qualitative researcher (qualitative component only) will be responsible for the consent process, which will be described in detail in the Trial Manual.

10.5 Co-enrolment

Patients who consent to participate in the MARS 2 study will be unable to participate in another interventional in mesothelioma study during the chemotherapy phase of the trial. Co-enrolment in a concurrent interventional study is allowed after either: 6 cycles of chemotherapy have been completed, or the patient has been deemed unable to tolerate 6 cycles of chemotherapy. This will be documented in the study CRFs. Patients already enrolled on another interventional study in mesothelioma prior to being approached for MARS 2 will be ineligible; this will be documented on the trial screening log. Co-enrolment in a concurrent observational study is not precluded.

11. Research governance

This study will be conducted in accordance with:

- International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
- Research Governance Framework for Health and Social Care

11.1 Sponsor approval

Any amendments to the trial documents must be approved by the Trial Sponsor prior to submission to the REC.

11.2 NHS approval

Approval from the local NHS Trust is required prior to the start of the trial at each site.

Any amendments to the trial documents approved by the REC/HRA will be submitted to the Trust for information or approval as required.

11.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or BTC (CTEU) or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved the REC that they receive and ensure that the changes are complied with.

11.4 Monitoring by Trial Sponsor

The study will be monitored and audited in accordance with the Trial Sponsor's policy, which is consistent with the Research Governance Framework. All study related documents will be made available on request for monitoring and audit by the Trial Sponsor, BTC (CTEU), the relevant REC and for inspection by other licensing bodies.

11.5 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG (96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

11.6 Clinical Trial Authorisation

Surgery consisting of (extended) pleurectomy decortication is not classed as an investigational medicinal product and a Clinical Trial Authorisation from the Medicines and healthcare products regulatory agency (MHRA) is not required.

12. Data protection and participant confidentiality

12.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 1998.

12.2 Data handling, storage and sharing

12.2.1 Data handling

Data will be entered into a purpose-designed SQL server database hosted on the NHS network. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to MARS 2 study staff. Information capable of identifying participants will not be made available in any form to those outside the study.

Access to the database will be via a secure password-protected web-interface. Study data transferred electronically between the University of Bristol and the NHS will only be transferred via a secure network in an encrypted form. Data transferred from the Coordinating Centre to the Health Economics team will also be transferred by secure means. The participants will be identified using their name and unique study identifier on the secure database. Other personal identifiers (address, postcode, contact number, NHS number) will be held in order that study patients may be contacted during follow-up and provided with a summary of the results at the end of the trial. These identifiers will be held securely in the database. Data extracted from the database for analysis and reporting purposes will not include personal identifiers. Participants will be identified by their study number only.

Data will be entered promptly and data validation and cleaning will be carried out throughout the trial. The trial manual will cover database use, data validation and data cleaning. The manual will be available and regularly maintained. Where electronic patient medical notes are used, local Trust policies will be followed.

Data will be submitted to the BTC (CTEU) either directly into the database, which will be accessed by via the NHS network, by fax, or by NHS.net email.

12.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Where trial related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the trial in accordance to BTC (CTEU) policy. In compliance with the MRC Policy on Data Sharing, relevant 'meta'-data about the trial and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely (University server). A secure electronic 'key' with a unique participant identifier,

and key personal identifiers (e.g. name, date of birth and NHS number) will also be held indefinitely, but in a separate file and in a physically different location (NHS hospital server). These will be retained because of the potential for the raw data to be used subsequently for secondary research.

12.2.3 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be retained for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body. Patient identifiers would not be passed on to any third party.

13. Dissemination of findings

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications (including a full report to the NIHR-HTA programme) and through patient organisations and newsletters to patients, where available.

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15. Amendments to protocol

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
9 (Substantial)	3.0	25 May 2017	4.0	3 October 2017	Protocol amended previously within the pilot phase as documented in REC/HRA amendment forms. Amendment 9 is to transition from pilot to full study.	28 October 2017
10 (Non-substantial)	4.0	3 October 2017	5.0	12 March 2018	Clarification of exclusion criteria (ECOG status, co-enrolment), safety reporting flow chart and the co-enrolment section.	NA
11, 12, & 13 (all Non-substantial amendments)	No changes to protocol					
14 (Substantial)	5.0	12 March 2018	6.0	10 April 2019	Various clarifications and errors corrected. ISRCTN number added. Length of follow up extended until the end of the study for all participants. Video-recording aspect of the surgical QA removed. Recruitment section tweaked to allow for the local variations in patient pathway at different sites. Use of	13 May 2019

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
					paper CRFs no longer mandatory.	
15 (Non-substantial)	No changes to the protocol					
16 (Substantial)	6.0	10 April 2019	7.0	16 March 2020	The pathology QA procedure has been added to the Trial Methods section, clarification of period to report SAEs and protocol updated with new name of the coordinating centre.	2 April 2020
17 (Non-Substantial)	No changes to the protocol					
18 (Non-Substantial)	No changes to the protocol					
19 (Non-Substantial)	7.0	16 March 2020	8.0	29 June 2020	The pathology QA procedure has been amended.	NA
20 (Non-Substantial)	No changes to the protocol					
21 (Non-Substantial)	8.0	29 June 2020	9.0	30 April 2021	Safety Reporting section clarified. Other minor changes clarifying length of follow up.	NA