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

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ABSTRACT

Introduction Mesothelioma remains a lethal cancer. To date, systemic therapy with pemetrexed and a platinum drug remains the only licensed standard of care. As the median survival for patients with mesothelioma is 12.1 months, surgery is an important consideration to improve survival and/or quality of life. Currently, only two surgical trials have been performed which found that neither extensive (extra-pleural pneumonectomy) or limited (partial pleurectomy) surgery improved survival (although there was some evidence of improved quality of life). Therefore, clinicians are now looking to evaluate pleurectomy decortication, the only radical treatment option left.

Methods and analysis The MARS 2 study is a UK multicentre open parallel group randomised controlled trial comparing the effectiveness and cost-effectiveness of surgery—(extended) pleurectomy decortication—versus no surgery for the treatment of pleural mesothelioma. The study will test the hypothesis that surgery and chemotherapy is superior to chemotherapy alone with respect to overall survival. Secondary outcomes include health-related quality of life, progression-free survival, measures of safety (adverse events) and resource use to 2 years. The Quintet Recruitment Intervention is integrated into the protocol to allow for recruitment.

Ethics and dissemination Research ethics approval was granted by London – Camberwell St. Giles Research Ethics Committee (reference 13/LO/1481) on 7 November 2013. We will submit the results for publication in a peer-reviewed journal.

Strengths and limitations of this study

► (Extended) pleurectomy decortication is currently offered to patients with mesothelioma on the United Kingdom National Health Service, but it is unknown whether it is a clinically beneficial or cost-effective treatment option. MARS 2 is the first randomised controlled trial to compare this type of surgery with no surgery in this patient population.

► Surgical quality assurance measures will be implemented to ensure that the intervention will be delivered at centres with expertise.

► Patients may come with a pre-conceived perception that surgery will be beneficial, which can lead to crossover (ie, patients allocated to no surgery may go on to seek surgery elsewhere). The integrated Quintet Recruitment Intervention supports recruitment staff in responding to patient preferences and conveying balanced information.

► It is not possible to blind participants or the study team, but the primary outcome (survival) is objective.

► Patient pathways vary at different sites. Some flexibility has been worked into the protocol to allow for this.
INTRODUCTION
In the UK, approximately 2500 patients are diagnosed each year with pleural mesothelioma, a treatment-resistant and lethal cancer of the membranes lining the outer surface of the lung and the inside of the chest wall primarily due to asbestos exposure. Deaths are increasing yearly and are estimated to peak this year. So far, most treatments have proven ineffective. The current standard of care, consisting of 4 to 6 cycles of platinum and pemetrexed chemotherapy, as recommended by the National Institute for Health and Care Excellence (NICE), has been associated with only an additional 3 months of survival. As the median survival for patients with mesothelioma is 12.1 months, surgery to remove as much of the disease as possible remains an important consideration to improve survival and/or health-related quality of life (HRQoL).

Pleurectomy decortication is the most common surgical procedure for mesothelioma worldwide and is defined as parietal and visceral pleurectomy to remove all gross tumour without diaphragm or pericardial resection. Extended pleurectomy decortication can also be carried out, when parietal and visceral pleurectomy is undertaken to remove all gross tumour, including the resection of the diaphragm and/or pericardium. In the document we use the term (extended) pleurectomy decortication to refer to either of the two procedures. The other main types of surgery for mesothelioma are extra-pleural pneumonectomy, which is defined as en bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium and diaphragm (in cases where the pericardium and/or diaphragm are not involved by tumour, these structures may be left intact); and partial pleurectomy, which is the partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes but leaving gross tumour behind.

So far, no advantage, in terms of survival, has been observed with any type of surgery in randomised controlled trials (RCTs) conducted to date. The MARS feasibility study (ISRCTN95583524), a trial of extra-pleural pneumonectomy with adjuvant haemothorax irradiation, concluded that surgery was unlikely to offer either an improvement to survival or HRQoL and possibly harmed patients. MesoVATS (ISRCTN34521019) concluded that partial pleurectomy did not improve survival, although it showed that patients in the better prognostic group had improved HRQoL after 6 months.

Suitable patients, both in the UK and internationally, are currently offered pleurectomy decortication as it is considered to carry less morbidity compared with the more extensive extra-pleural pneumonectomy but still achieves complete macroscopic resection which partial pleurectomy does not. However, we do not know if (extended) pleurectomy decortication in conjunction with chemotherapy will improve survival compared with the current standard of care (chemotherapy alone). In the absence of RCTs, (extended) pleurectomy decortication may continue to be offered despite a lack of high-quality evidence of clinical efficacy or any evidence on cost-effectiveness.

Aims and objectives
MARS 2 is a UK-wide multicentre RCT which will test the hypothesis that (extended) pleurectomy decortication and chemotherapy is superior to chemotherapy alone with respect to overall survival for patients with pleural mesothelioma.

Specific objectives are to estimate:
A. The difference between groups in overall survival.
B. The difference between groups with respect to a range of secondary outcomes including HRQoL, progression-free survival and measures of safety (adverse health events).
C. The cost-effectiveness of (extended) pleurectomy decortication compared with no surgery.

METHODS AND ANALYSIS
Trial design
MARS 2 is a multicentre, non-blinded parallel two-group, pragmatic RCT of surgery and chemotherapy versus chemotherapy alone for suitable patients with mesothelioma.

An internal pilot funded by Cancer Research UK (award ref: C27967/A15895) and coordinated by the Papworth Trials Unit Collaboration demonstrated the feasibility of recruitment across 14 medical sites and 2 joint medical and surgical sites of excellence, as the target of 50 participants recruited within a 24-month period was achieved.

Since the end of the pilot phase in December 2016, an additional eight medical, one surgical, and two joint medical and surgical sites have been opened for the full trial. In addition, the full trial will provide recruiting sites with the support of an integrated QuinteT Recruitment Intervention (QRI)12–14 to optimise recruitment and retention.

Setting, centre and surgeon eligibility
This study is taking place in National Health Service (NHS) secondary care centres, including teaching and district general hospitals.

To be eligible as a medical site, the centre must:
1. Be an NHS Trust with access to a multidisciplinary team (MDT) to discuss patients with mesothelioma.
2. Have a track record of treating patients with mesothelioma.

To be eligible as a surgical site, the centre must:
1. Be an NHS Trust with an established mesothelioma MDT.
2. Have a minimum of two named mesothelioma surgeons participating in the trial.

All surgeons participating in the full trial must be accredited by (1) self-reporting a minimum of five cases in which they have performed (extended) pleurectomy decortication, (2) observing the procedure being undertaken at an established MARS 2 surgical site, (3) having a surgeon from the pilot phase observe their first MARS
2 procedure undertaken and (4) having one randomly selected MARS 2 operation between procedures 5 and 10 observed by a surgeon from the pilot phase to ensure fidelity.

Patients from all medical (only) sites are referred to a trial-accredited surgical site for CT assessment of eligibility, further discussion about the study and surgery (if randomised to this group).

**Trial population**

The target population are patients with a diagnosis of epithelioid, sarcomatoid or biphasic mesothelioma. Patients will be eligible to take part if ALL of the following apply:

- Adult aged ≥16 years of age.
- Tissue (cytology or histology) confirmed epithelioid, sarcomatoid or biphasic mesothelioma, as reviewed by MDT to be of sufficient certainty to recommend chemotherapy as treatment.
- Disease confined to one hemithorax based on CT assessment.
- Disease deemed surgically resectable by a surgeon at a MARS 2 surgical site.
- Deemed fit for surgery by a surgeon at a MARS 2 surgical site.
- Capacity to provide written informed consent to participate in the trial.

Patients will not be eligible if they have:

- Severe shortness of breath (Eastern Cooperative Oncology Group status ≥2, or preoperative FEV1 or TLco less than 20%).
- Severe heart failure (NYHA III or IV, or ejection fraction less than 30% by echocardiogram).
- End-stage kidney failure requiring dialysis.
- Liver failure (eg, encephalopathy and/or coagulation abnormalities).
- Any other serious concomitant disorder that would compromise participant safety during surgery.
- Prisoner.
- Patient lacks capacity to consent.
- Existing co-enrolment in another interventional study that aims to improve survival.

**Patient approach, consent and randomisation**

The local research team at the medical site will take written informed consent from participants. In addition to the main study, the team may also seek consent for audio-recording of consultations and participation in interviews, for QRI purposes. Participants will then receive two cycles of chemotherapy (standard care) and have a further CT scan to confirm eligibility (ie, disease still resectable) before being randomised, using a secure web-based randomisation system (Sealed Envelope https://sealedenvelope.com).

Participants will be randomised in a 1:1 ratio. Minimisation (with a random component) will be applied for selected baseline variables (age, performance status and cell type) that influence survival, in addition to stratification by recruiting site to ensure that the cohorts are as balanced as possible.

**Trial interventions**

Patients will be randomised to receive one of the following interventions:

- (Extended) pleurectomy decortication and chemotherapy: two cycles of platinum and pemetrexed chemotherapy followed by surgery and then up to four cycles of the same chemotherapy.
- Chemotherapy alone (control intervention): up to six cycles of platinum and pemetrexed chemotherapy alone (current standard of care).

The trial schema is illustrated in figure 1.

After randomisation, any changes in the choice of chemotherapy, addition of other agents or entry into therapeutic trials (eg, immunotherapies) will be permitted for patients with progressive disease. At the time of trial design, there was no national consensus on postoperative prophylactic radiotherapy, so it was decided that irradiation to thoracic procedure sites may be undertaken for MARS 2 patients. Patients in both groups can also receive further surgery, including thoracic, if it is without radical intent. The aim is to conduct a pragmatic trial while closely monitoring uptake of additional therapies, studies or surgeries in order to account for them in the trial analyses, if required.

**Primary and secondary outcomes**

The primary outcome is survival, calculated from randomisation date (randomisation occurs after the first two cycles of chemotherapy). All participants will be followed up to the end of the trial (minimum of 2 years after randomisation).

Secondary outcomes have been selected to assess the efficacy of the two approaches. Secondary outcomes are (1) progression-free survival to the end of the trial (minimum of 2 years after randomisation); (2) serious adverse health events to 2 years after randomisation; (3) disease-specific and generic HRQoL using the following validated questionnaires—European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), to assess the HRQoL of patients with cancer, and EuroQol EQ-5D-5L.15 16 a widely used generic measure of HRQoL (both of these will be measured at baseline, pre-randomisation, and 6 weeks, 6, 12, 18 and 24 months post-randomisation); and (4) healthcare resource use to the end of the study: chemotherapy cycles and initial surgical admission (for chemotherapy plus surgery group), and further resources measured at 6 weeks post-randomisation then every 6 months, with a final follow-up at the end of the study if not followed up in the previous 4 months.

**Data collection**

The schedule for data collection for the study is shown in table 1. Data will be collected onto purpose-designed case report forms (CRFs) and participant-completed...
questionnaires and entered onto a bespoke database for data cleaning and analysis. Access to the database will be via a secure password-protected web interface hosted on an NHS server. Data about adverse events will be collected and reported in accordance with sponsor’s and regulatory requirements.

**Risk of bias**
Participants and clinical personnel cannot be blinded to allocation due to the nature of the study intervention. However, standard local protocols will be followed in terms of patient care. The patient information leaflet and conversations with MARS 2 site staff will describe and balance the potential benefits and risks of both having and not having surgery. Therefore, this approach will reduce participant’s expectations that one or other treatment protocol will lead to a more favourable result.

In addition, the study’s primary outcome is an objective measure (survival), and clear definitions of each secondary outcome measure will be provided to trial personnel. The HRQoL follow-up questionnaires may be more at risk of bias than other measures, but patients will not have had this surgery previously and as such should not have any expectation regarding its effect on their HRQoL. Missing outcome data will be minimised, as survival and progression-free survival data can be obtained from hospital records. Losses to follow-up will be minimised by maintaining regular contact with participants (by telephone and post) to complete follow-up questionnaires. Non-adherence to randomised allocation will be documented. Bias in the reported results will be minimised by having pre-specified outcomes in the trial protocol and a pre-specified analysis plan.

**Sample size**
The total sample size has been set at 328 participants (164 per group). The patients randomised in the pilot trial will contribute to the total sample size. The study will have 80% power to detect a HR of 0.7 at 5% statistical significance (two-sided), modelled on a published assumption of a median survival time of 16.8 months in patients with mesothelioma who were fit enough to receive surgery, but did not have it and allowing for 10% cross-over from the medical to surgery groups (as noted in previous trials such as MARS). Cross-over will be minimised through instruction (ie, recruit only patients who have equipoise from the outset) and education.
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*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.
The relative difference of 30% (HR 0.7) 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. The possibility that survival could be worse with surgery was also discussed, and a relative difference of 30% was also regarded as an appropriate difference to indicate harm, therefore a two-tailed test for superiority was agreed.

**Patient and public involvement**

Patient and public representatives were involved from inception and advised on the trial design of MARS 2, the identification of the choice of the primary outcome and defined the minimally important difference in relative survival.

The study team have continuing engagement with the Royal Brompton Hospital Cancer Consortia PPI group, which consists of patients and carers who have undergone surgery for lung cancer and mesothelioma, to advise on patient-orientated questions that arise from the trial conduct. One patient from the PPI group, a mesothelioma survivor, has agreed to sit on the Trial Steering Committee. The PPI group will also be involved in the dissemination of study results.

**Integrated QRI**

Recruitment to RCTs can be challenging, particularly for surgical trials. An integrated QRI will therefore be employed during the main study phase to optimise recruitment and retention. 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.

A multi-faceted, flexible approach will be used to investigate site-specific or wider recruitment obstacles. These will comprise the following:

- Mapping of eligibility and recruitment pathways to collate basic data about the levels of eligibility and recruitment, and identify points at which patients opt in or out of the trial.
- In-depth, semi-structured interviews with a purposive sample of staff members involved with aspects of trial design/management and recruitment across centres, and patients eligible for recruitment to the trial. Interviews will explore participants’ perspectives of the trial, views on the presentation of study information, understanding of trial processes (eg, randomisation), and reasons underlying decisions to accept or decline the trial. In addition, interviews with staff and other individuals involved in the trial will explore perspectives on the trial design and protocol, views about the evidence on which the trial is based, perceptions of uncertainty/equipoise for themselves and their colleagues, methods for identifying eligible patients, views on eligibility, and examples of actual recruitment successes and difficulties. Interview topic guides will be used to ensure similar topic areas are covered across interviews, while still providing the scope for participants to raise issues of pertinence to them.
- Audio-recording of consultations between healthcare staff and potentially eligible patients across centres to understand the recruitment process at each centre and to identify and investigate the challenges to recruitment. The QRI researcher will listen to and qualitatively analyse the appointments, documenting instances such as unclear, insufficient or imbalanced information provision and unintentional transferring of clinician treatment preferences to patients.
- Observation of Trial Management Group (TMG) and investigator meetings to gain an overview of trial conduct and overarching challenges (logistical issues, etc).

An account of the anonymised findings from all the data will be fed back to the Chief Investigator and TMG. The data will be used by the QRI to provide supportive and confidential individual and group feedback to recruiters to help them to communicate equipoise, balance treatment options and explain to patients the benefits and purposes of trial participation, while optimising informed consent.

**Statistical analyses**

The data will be analysed for randomised patients according to intention to treat and follow Consolidated Standards of Reporting Trials (CONSORT) guidelines. Analyses will be adjusted for site and for design factors included in the cohort minimisation (eg, age, performance status and cell type).

Survival time and progression-free survival time from randomisation 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. Patient-reported outcome scores (HRQoL EQ-5D-5L and QLQ-C30) will be compared using a mixed regression model and adjusted for baseline measures where appropriate. Changes in treatment effect with time will be assessed by adding a treatment × time interaction to the model and comparing models using a likelihood ratio test. Deaths will be accounted for by modelling survival and HRQoL jointly. Model fit will be assessed using standard methods and alternative models and/or transformations will be explored if appropriate. Treatment differences and 95% CIs will be reported.

Missing data on patient questionnaires will be dealt with according to the scoring manuals. Multiple imputation methods will be used if greater than 5% of cases have missing data, otherwise complete case analysis will be undertaken. Compliance rates will be reported, including the number of participants who have withdrawn from the study, have been lost to follow-up or died. Causes of death for trial participants will be recorded.

Frequencies of adverse events will be described. The proportion of participants experiencing one or more
serious adverse events in the follow-up period will be compared using a generalised linear model.

Two subgroup analyses are planned: (1) comparing primary and secondary outcomes by the experience level of the surgical site; (2) comparing the primary outcome by type of mesothelioma (epithelioid, sarcomatoid or biphasic). An exploratory analysis investigating the effect of surgeon (surgical group only) will be performed for the primary outcome.

No interim analyses are planned. The primary analysis will take place when follow-up is complete for all recruited participants.

Economic evaluation
The economic evaluation will compare the costs and effects of surgery versus no surgery, following established guidelines as set out by NICE.20 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 at each follow-up timepoint.5,16 Resource use data collection will be integrated into the trial CRFs for chemotherapy cycles and surgery (if applicable, this will include details of the surgical procedure, length of stay in hospital by level of care, and postoperative complications) and be collected at each follow-up timepoint.

Unit costs will be sought to value resource use data, and the total costs per participant calculated. Responses to the EQ-5D-5L will be assigned valuations according to NICE guidance at the time of analysis,21 and combined with survival to calculate QALYs gained per participant. Missing resource use and EQ-5D-5L data will be handled using multiple imputation methods.22 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 surgery compared with no surgery. Sensitivity analyses will assess the impact of varying key parameters on baseline cost-effectiveness results. Results will be expressed in terms of a cost-effectiveness acceptability curve, which indicates the likelihood that surgery is cost-effective for different levels of willingness to pay for health gain.

Ethics and dissemination
The study intervention is already routinely used in the NHS. The pilot study was managed by Papworth Trials Unit Collaboration and the main trial is managed by the Bristol Trials Centre Clinical Trials and Evaluation Unit and sponsored by Royal Brompton & Harefield NHS Foundation Trust. Each participant has the right to withdraw at any time. In addition, the investigator may withdraw the participant from their allocated treatment group if a clinical reason for not performing the surgical intervention is discovered. If a participant wishes to withdraw, any data already collected will be included in the study analyses, unless the participant expresses a wish for their data to be excluded. Withdrawing patients will be asked if they would continue in follow-up and complete the requisite questionnaires. Participants who choose to withdraw from the study will be treated according to their hospital's standard procedures.

The findings will be disseminated by usual academic channels, that is, presentation at international meetings and peer-reviewed publications. A full report for the funder will be written on completion of the study and a lay summary of the results provided to patients.

Major changes to protocol
Since the first study protocol was approved by the Research and Ethics Committee (the current version is V.6.0, 10 April 2019), the following changes have been made:

► Qualitative assessment substudy added, as part of the pilot phase only.
► The EuroQol EQ-5D-5L was added.
► Updates to transition from pilot phase to main study, including addition of the integrated QRI and economic evaluation, and removal of the collection of blood and tissue samples, and one of the disease-specific questionnaires—the EORTC QLQ LC13.
► Length of follow-up extended from 2 years until the end of the study for all participants to ensure that the study has 80% power.
► Video-recording aspect of the surgical quality assurance removed as this was deemed impractical by sites, and it was agreed that it was unnecessary by the Data Safety and Monitoring Committee and the Trial Steering Committee, acknowledging the other surgical quality assurance measures that are in place.

Study progress
Recruitment started in May 2015 and 308 patients have been randomised so far (correct on 25 May 2020). A total of 66 patients from the pilot study are included in this figure. Recruitment will continue until 30 September 2020.

The full protocol is available online (https://www.journalslibrary.nihr.ac.uk/programmes/hta/1518831/).

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Unless otherwise stated above, committee members have declared no competing interests. Independent Data Monitoring and Safety Committee members: Linda Sharples, Valerie Rusch, Mark Britton, Robin Rudd, Joseph S Friedberg, Peter Goldstraw. Unless otherwise stated above, committee members have declared no competing interests.

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REFERENCES