BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038892
Article Type:	Protocol
Date Submitted by the Author:	27-Mar-2020
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Keywords:	ONCOLOGY, CHEMOTHERAPY, Thoracic surgery < SURGERY, THORACIC MEDICINE

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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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WORD COUNT: 3739 (excluding title page, abstract, references, figures and tables)

Number of figures: 1

Number of tables: 1

KEYWORDS: Randomised controlled trial; mesothelioma; surgery; radical surgery; pleurectomy decortication; cancer

ABSTRACT

Introduction: Mesothelioma remains a lethal cancer. To date, systemic therapy with pemetrexed and a platinum drug remains the only licenced standard of care. As the median survival for mesothelioma patients 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 trial to optimise recruitment.

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

Trial registration numbers: ISRCTN – ISRCTN44351742 and ClinicalTrials.gov – NCT02040272.

ARTICLE SUMMARY

Strengths and limitations of this study

- 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 crossovers (i.e. 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 United Kingdom (UK), approximately 2,500 patients are diagnosed each year with pleural mesothelioma,[1] 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.[2] 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)[3], has been associated with only an additional 3 months of survival.[4] As the median survival for mesothelioma patients is 12.1 months,[4] 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).[5]

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.[6] '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. The other main types of surgery for mesothelioma are: i) 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.[6]

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.[7] MesoVATS (ISRCTN34321019) concluded that partial pleurectomy did not improve survival, although it showed that patients in the better prognostic group, had improved HRQoL after 6 months.[8]

Suitable patients, both in the UK and internationally, are currently offered pleurectomy decortication as it is considered to carry less morbidity compared to the more extensive extra-pleural pneumonectomy but still achieves complete macroscopic resection which partial pleurectomy does not.[9-11] However, we do not know if pleurectomy decortication in conjunction with chemotherapy will improve survival compared to the current standard of care (chemotherapy alone). In the absence of RCTs, 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 to 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 8 medical, 1 surgical and 2 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:

i) be an NHS Trust with access to a multidisciplinary team (MDT) to discuss patients with mesothelioma;
ii) have a track record of treating patients with mesothelioma

To be eligible as a surgical site, the centre must:

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

All surgeons participating in the full trial must be accredited by; i) self-reporting a minimum of 5 cases in which they have performed (extended) pleurectomy decortication; ii) observing the procedure being undertaken at an established MARS 2 surgical site; iii) having a surgeon from the pilot phase observe their first MARS 2 procedure undertaken; and iv)

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 computed tomography (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 hemi-thorax 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 (ECOG) status ≥ 2; or pre-operative forced expiratory volume after one second (FEV1) or transfer factor of the lung for carbon monoxide (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 (e.g. 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 (i.e. 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:

- *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 (e.g. immunotherapies) will be permitted for patients with progressive disease. At the time of trial design, there was no national consensus on post-operative 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 whilst 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. All participants will be followed up to the end of the trial (minimum of two 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 two years after randomisation); 2) serious adverse health events to two 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 cancer patients; 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.

Table 1 Data collection

	Pre-randomisation				Post-randomisation							
	Screening	Baseline	2 cycles chemo-therapy	End of chemo-therapy cycle 2	Surgical admission *	Up to 4 cycles chemo-therapy	Follow-up					
							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							✓	✓	✓	✓	✓	✓

* 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

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 hazard ratio (HR) of 0.7 at 5% statistical significance (2-sided), modelled on a published assumption of a median survival time of 16.8 months in mesothelioma patients who were fit enough to receive surgery, but did not have it[17] and allowing for 10% cross-over from the medical to surgery groups (as noted in previous trials such as MARS 1[7]). Cross-over will be minimised through instruction (i.e. recruit only patients who have equipoise from the outset) and education.

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% 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 that 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 QuinteT Recruitment Intervention (QRI)

Recruitment to RCTs can be challenging[18], particularly for surgical trials.[19] 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 (e.g. 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 team 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, whilst 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 (e.g. 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, 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 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% confidence intervals 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 two-year follow-up period will be compared using a generalised linear model.

Two subgroup analyses are planned: i) comparing primary and secondary outcomes by the experience level of the surgical site; and ii) 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.[15 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 post-operative 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 to 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. This study has been reviewed and given favourable opinion by the London - Camberwell St. Giles Research Ethics Committee (REC; reference 13/LO/1481) on 7th November 2013. 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 hospitals' standard procedures.

The findings will be disseminated by usual academic channels, i.e. 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 REC (the current version is v6.0, 10 April 2019), the following changes have been made:

- Qualitative assessment sub-study 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 LC-13.
- Length of follow up extended from two 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.

The relevant regulatory approvals were obtained for amendments to the protocol. Relevant parties (eg, investigators, trial participants) were informed.

Study progress

Recruitment started in May 2015 and 304 patients have been randomised so far (correct on 25 March 2020). 66 patients from the pilot study are included in this figure. Recruitment will continue until 1st June 2020.

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

ADDITIONAL FIGURES

Figure 1. Trial schema showing the recruitment pathway for the MARS 2 study

ABBREVIATIONS

CONSORT- Consolidated Standards of Reporting Trials
CRF – Case Report Form
CT- computed tomography
ECOG- Eastern Cooperative Oncology Group
EORTC- European Organisation for Research and Treatment of Cancer
FEV1- forced expiratory volume after one second
HR- hazard ratio
HRQoL- health related quality of life
ISRCTN - International Standard Randomised Controlled Trials Number
MDT – multidisciplinary team
NHS- National Health Service
NICE- National Institute for Health and Care Excellence
NIHR- National Institute for Health Research
NYHA – New York Heart Association
PPI- patient and public involvement
QALY- quality adjusted life years
QLQ- quality of life questionnaire
QuinteT – Qualitative research integrated within trials
QRI- QuinteT Recruitment Intervention
RCT- randomised controlled trial
REC- Research Ethics Committee
TLco- transfer factor of the lung for carbon monoxide
TMG – Trial Management Group
UK- United Kingdom

Acknowledgements
The MARS 2 trial is sponsored by The Royal Brompton and Harefield NHS Foundation Trust. The sponsor will be responsible for the oversight of the MARS 2 study and to ensure the trial is managed appropriately. We want to thank the large teams at each hospital who work on the MARS 2 study (representatives from each are listed below). We would also like to thank Dr Fiona McDonald from the Royal Marsden Hospital, Dr Nagmi Qureshi from Papworth Hospital and Professor Simon Padley from the Royal Brompton Hospital for their radiotherapy advisory roles. Thank you also to Professor Andrew Nicholson for his histopathology advisory role for MARS 2.

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Unless otherwise stated above, committee members have declared no competing interests.

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EL - Study design, preparation and drafting of protocol and manuscript, Chief Investigator for the trial; LD - Study design, preparation of protocol and review of manuscript; JGE - Study design, preparation of protocol and review of manuscript, Principal Investigator and acquired data for the study; DE - Design of integrated qualitative study, preparation of study protocol, review of manuscript; DAF - Study design, preparation of protocol and review of manuscript,

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Funding

This research is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (project number 15/188/31). The pilot study was funded by Cancer Research UK and Mesothelioma UK has contributed towards patient travel expenses.

This study was designed and delivered in collaboration with the Bristol Trials Centre Clinical Trials and Evaluation Unit (CTEU), a UK Clinical Research Collaboration (UKCRC) registered clinical trials unit which, as part of the Bristol Trials Centre (BTC), is in receipt of NIHR Clinical Trials Unit (CTU) support funding.

Daisy Elliott was supported by the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.
Sanjay Popat acknowledges NHS funding to the Royal Marsden Hospital / Institute of Cancer Research NIHR Biomedical Research Centre.

Disclaimer
The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health and Social Care.

The funder and sponsor approve any amendments to the study but have no direct involvement in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to Submit this report for publication.

Competing interests' statement
EL: reports personal fees from Abbott Molecular, personal fees from Glaxo Smith Kline, personal fees from Pfizer, personal fees from Norvatis, personal fees from Covidien, personal fees from Roche, personal fees from Lily Oncology, personal fees from Boehringer Ingelheim, personal fees from Medela, grants and personal fees from ScreenCell, personal fees from Ethicon, grants from Clearbridge Biomedics, grants from Illumina, grants from Guardant Health, personal fees from AstraZenecia (outside the submitted work), a patent P52435GB issued to Imperial Innovations, and a patent P57988GB issued to Imperial Innovations and Director of lung screening at Cromwell Hospital, CI for VIOLET NIHR HTA (13/04/03), CI for MARS 2 NIHR HTA (15/188/31); DAF: reports grants from Astex Therapeutics, personal fees from Aldeyra, grants from Boehringer Ingelheim, non-financial support from Clovis, non-financial support from Eli Lilly, from BMS, personal fees from Inventiva, personal fees from Paredox, personal fees and non-financial support from Roche, grants from MSD, grants from Bayer, during the conduct of the study; SP: reports personal fees from BMS, personal fees from Roche, personal fees from Takeda, personal fees from AstraZeneca, personal fees from Pfizer, personal fees from MSD, personal fees from EMD Serono, personal fees from Guardant Health, personal fees from Abbvie, personal fees from Boehringer Ingelheim, personal fees from OncLive, personal fees from Medscape, personal fees from Incyte (outside the submitted work); PK: reports non-Financial Support: Travel grant to ESMO Congress 2018, was sponsored by Boeringer Ingelheim, West Midlands UK Oncology Specialist Trainee Regional Training Day April 2018, meeting was sponsored by Roche, Servier and Bristol Myers Squibb in the purchase of exhibition stand space, Eisai was sponsoring this meeting towards the cost of catering. TM: reports other from MSD, other from Roche, other from Tesaro, from AstraZeneca, personal fees from Tesaro, personal fees from Roche, personal fees from MSD, personal fees from Amgen, other from BMS (outside the submitted work); KA: reports grants from NIHR HTA, during the conduct of the study; RAH: reports grants from NIHR HTA, during the conduct of the study; KJ: reports grants from NIHR HTA, during the conduct of the study; ES: reports grants from UK National Institute for Health Research (Health Technology Assessment Programme), Department of Health and Social Care, during the conduct of the study; CAR: reports grants from National Institute for Health Research, during the conduct of the study.

Unless otherwise stated above, authors have declared no competing interests.

Patient Consent for publication
Not required.

Ethics Approval

This study received a favourable opinion by the London - Camberwell St. Giles Research Ethics Committee (REC; reference 13/LO/1481) on 7th November 2013.

Provenance and peer review
Not commissioned, externally peer reviewed.

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 prior consent having been given by the patients and assurance from the secondary researcher that the proposed use of the data is compliant with the Medical Research Council (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.

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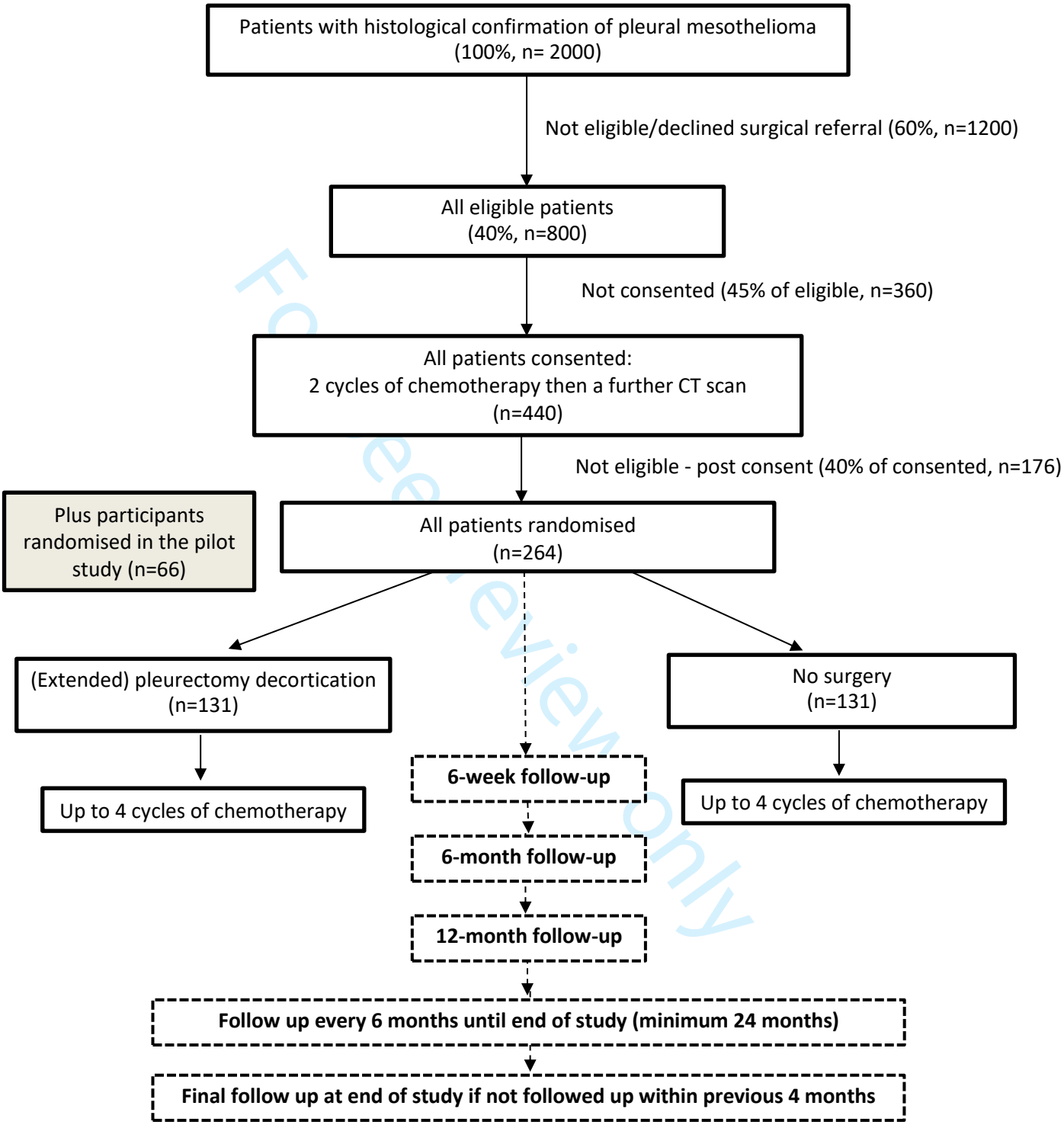
Figure 1 **Trial schema showing the recruitment pathway for the MARS 2 study**



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3,23
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6,7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7,8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8,9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8,9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7,8, 13,14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12,13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12-14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10,11,12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14-16

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14,15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15,16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	25
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23, 24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	25
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	4, 16
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	On request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038892.R1
Article Type:	Protocol
Date Submitted by the Author:	27-May-2020
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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Surgery
Keywords:	ONCOLOGY, CHEMOTHERAPY, Thoracic surgery < SURGERY, THORACIC MEDICINE

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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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WORD COUNT: 3703 (excluding title page, abstract, references, figures and tables)

Number of figures: 1

Number of tables: 1

KEYWORDS: Randomised controlled trial; mesothelioma; surgery; radical surgery; pleurectomy decortication; cancer

ABSTRACT

Introduction: Mesothelioma remains a lethal cancer. To date, systemic therapy with pemetrexed and a platinum drug remains the only licenced standard of care. As the median survival for mesothelioma patients 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 trial to optimise recruitment.

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

Trial registration numbers: ISRCTN – ISRCTN44351742 and ClinicalTrials.gov – NCT02040272.

ARTICLE SUMMARY

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 crossovers (i.e. 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 United Kingdom (UK), approximately 2,500 patients are diagnosed each year with pleural mesothelioma,[1] 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.[2] 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)[3], has been associated with only an additional 3 months of survival.[4] As the median survival for mesothelioma patients is 12.1 months,[4] 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).[5]

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.[6] 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.[6]

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.[7] MesoVATS (ISRCTN34321019) concluded that partial pleurectomy did not improve survival, although it showed that patients in the better prognostic group, had improved HRQoL after 6 months.[8]

Suitable patients, both in the UK and internationally, are currently offered pleurectomy decortication as it is considered to carry less morbidity compared to the more extensive extra-pleural pneumonectomy but still achieves complete macroscopic resection which partial pleurectomy does not.[9-11] However, we do not know if (extended) pleurectomy decortication in conjunction with chemotherapy will improve survival compared to 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 to 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 8 medical, 1 surgical and 2 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:

i) be an NHS Trust with access to a multidisciplinary team (MDT) to discuss patients with mesothelioma;
ii) have a track record of treating patients with mesothelioma

To be eligible as a surgical site, the centre must:

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

All surgeons participating in the full trial must be accredited by; i) self-reporting a minimum of 5 cases in which they have performed (extended) pleurectomy decortication; ii) observing the procedure being undertaken at an established MARS 2 surgical site; iii) having a surgeon from the pilot phase observe their first MARS 2 procedure undertaken; and iv)

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 computed tomography (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 hemi-thorax 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 (ECOG) status ≥ 2; or pre-operative forced expiratory volume after one second (FEV1) or transfer factor of the lung for carbon monoxide (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 (e.g. 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 (i.e. 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 (e.g. immunotherapies) will be permitted for patients with progressive disease. At the time of trial design, there was no national consensus on post-operative 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 whilst 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 two 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 two years after randomisation); 2) serious adverse health events to two 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 cancer patients; 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.

Table 1 Data collection

	Pre-randomisation				Post-randomisation							
	Screening	Baseline	2 cycles chemo-therapy	End of chemo-therapy cycle 2	Surgical admission *	Up to 4 cycles chemo-therapy	Follow-up					
							6 w	6 m	12 m	18 m	24 m	Every 6 m and end of trial**
Screening log	*ü*			*ü*								
CT scan	*ü***			*ü*								
Informed consent		*ü*										
Demography, medical history, blood test results		*ü*										
Lung function tests	*ü*	*ü****										
HRQoL		*ü*		*ü*			*ü*	*ü*	*ü*	*ü*	*ü*	
Chemotherapy treatment given***			*ü*			*ü*						
Surgery and in hospital post-operative data*****					*ü*							
Adverse events					*ü*		*ü*	*ü*	*ü*	*ü*	*ü*	
Patient reported resource and health service use							*ü*	*ü*	*ü*	*ü*	*ü*	*ü*

* 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

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 hazard ratio (HR) of 0.7 at 5% statistical significance (2-sided), modelled on a published assumption of a median survival time of 16.8 months in mesothelioma patients who were fit enough to receive surgery, but did not have it[17] and allowing for 10% cross-over from the medical to surgery groups (as noted in previous trials such as MARS 1[7]). Cross-over will be minimised through instruction (i.e. recruit only patients who have equipoise from the outset) and education.

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% 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 that 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 QuinteT Recruitment Intervention (QRI)

Recruitment to RCTs can be challenging[18], particularly for surgical trials.[19] 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 (e.g. 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 team 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, whilst 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 (e.g. 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, 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 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% confidence intervals 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 two-year follow-up period will be compared using a generalised linear model.

Two subgroup analyses are planned: i) comparing primary and secondary outcomes by the experience level of the surgical site; and ii) 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.[15 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 post-operative 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 to 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. This study has been reviewed and given favourable opinion by the London - Camberwell St. Giles Research Ethics Committee (REC; reference 13/LO/1481) on 7th November 2013. 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 hospitals' standard procedures.

The findings will be disseminated by usual academic channels, i.e. 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 REC (the current version is v6.0, 10 April 2019), the following changes have been made:

- Qualitative assessment sub-study 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 LC-13.

- Length of follow up extended from two 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 304 patients have been randomised so far (correct on 25 March 2020). 66 patients from the pilot study are included in this figure. Recruitment will continue until 1st June 2020.

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

ADDITIONAL FIGURES

Figure 1. Trial schema showing the recruitment pathway for the MARS 2 study

ABBREVIATIONS

CONSORT- Consolidated Standards of Reporting Trials
CRF – Case Report Form
CT- computed tomography
ECOG- Eastern Cooperative Oncology Group
EORTC- European Organisation for Research and Treatment of Cancer
FEV1- forced expiratory volume after one second
HR- hazard ratio
HRQoL- health related quality of life
ISRCTN - International Standard Randomised Controlled Trials Number
MDT – multidisciplinary team
NHS- National Health Service
NICE- National Institute for Health and Care Excellence
NIHR- National Institute for Health Research
NYHA – New York Heart Association
PPI- patient and public involvement
QALY- quality adjusted life years
QLQ- quality of life questionnaire
QuinteT – Qualitative research integrated within trials
QRI- QuinteT Recruitment Intervention
RCT- randomised controlled trial
REC- Research Ethics Committee
TLco- transfer factor of the lung for carbon monoxide
TMG – Trial Management Group

UK- United Kingdom

Acknowledgements
The MARS 2 trial is sponsored by The Royal Brompton and Harefield NHS Foundation Trust. The sponsor will be responsible for the oversight of the MARS 2 study and to ensure the trial is managed appropriately. We want to thank the large teams at each hospital who work on the MARS 2 study (representatives from each are listed below). We would also like to thank Dr Fiona McDonald from the Royal Marsden Hospital, Dr Nagmi Qureshi from Papworth Hospital and Professor Simon Padley from the Royal Brompton Hospital for their radiotherapy advisory roles. Thank you also to Professor Andrew Nicholson for his histopathology advisory role for MARS 2.

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Funding
This research is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (project number 15/188/31). The pilot study was

funded by Cancer Research UK and Mesothelioma UK has contributed towards patient travel expenses.

This study was designed and delivered in collaboration with the Bristol Trials Centre Clinical Trials and Evaluation Unit (CTEU), a UK Clinical Research Collaboration (UKCRC) registered clinical trials unit which, as part of the Bristol Trials Centre (BTC), is in receipt of NIHR Clinical Trials Unit (CTU) support funding.

Daisy Elliott was supported by the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.
Sanjay Popat acknowledges NHS funding to the Royal Marsden Hospital / Institute of Cancer Research NIHR Biomedical Research Centre.

Disclaimer

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health and Social Care.

The funder and sponsor approve any amendments to the study but have no direct involvement in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to Submit this report for publication.

Competing interests' statement

EL: reports personal fees from Abbott Molecular, personal fees from Glaxo Smith Kline, personal fees from Pfizer, personal fees from Norvatis, personal fees from Covidien, personal fees from Roche, personal fees from Lily Oncology, personal fees from Boehringer Ingelheim, personal fees from Medela, grants and personal fees from ScreenCell, personal fees from Ethicon, grants from Clearbridge Biomedics, grants from Illumina, grants from Guardant Health, personal fees from AstraZenecia (outside the submitted work), a patent P52435GB issued to Imperial Innovations, and a patent P57988GB issued to Imperial Innovations and Director of lung screening at Cromwell Hospital, CI for VIOLET NIHR HTA (13/04/03), CI for MARS 2 NIHR HTA (15/188/31); DAF: reports grants from Astex Therapeutics, personal fees from Aldeyra, grants from Boehringer Ingelheim, non-financial support from Clovis, non-financial support from Eli Lilly, from BMS, personal fees from Inventiva, personal fees from Paredox, personal fees and non-financial support from Roche, grants from MSD, grants from Bayer, during the conduct of the study; SP: reports personal fees from BMS, personal fees from Roche, personal fees from Takeda, personal fees from AstraZeneca, personal fees from Pfizer, personal fees from MSD, personal fees from EMD Serono, personal fees from Guardant Health, personal fees from Abbvie, personal fees from Boehringer Ingelheim, personal fees from OncLive, personal fees from Medscape, personal fees from Incyte (outside the submitted work); PK: reports non-Financial Support: Travel grant to ESMO Congress 2018, was sponsored by Boeringer Ingelheim, West Midlands UK Oncology Specialist Trainee Regional Training Day April 2018, meeting was sponsored by Roche, Servier and Bristol Myers Squibb in the purchase of exhibition stand space, Eisai was sponsoring this meeting towards the cost of catering. TM: reports other from MSD, other from Roche, other from Tesaro, from AstraZeneca, personal fees from Tesaro, personal fees

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Patient Consent for publication
Not required.

Ethics Approval
This study received a favourable opinion by the London - Camberwell St. Giles Research Ethics Committee (REC; reference 13/LO/1481) on 7th November 2013.

Provenance and peer review
Not commissioned, externally peer reviewed.

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 prior consent having been given by the patients and assurance from the secondary researcher that the proposed use of the data is compliant with the Medical Research Council (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.

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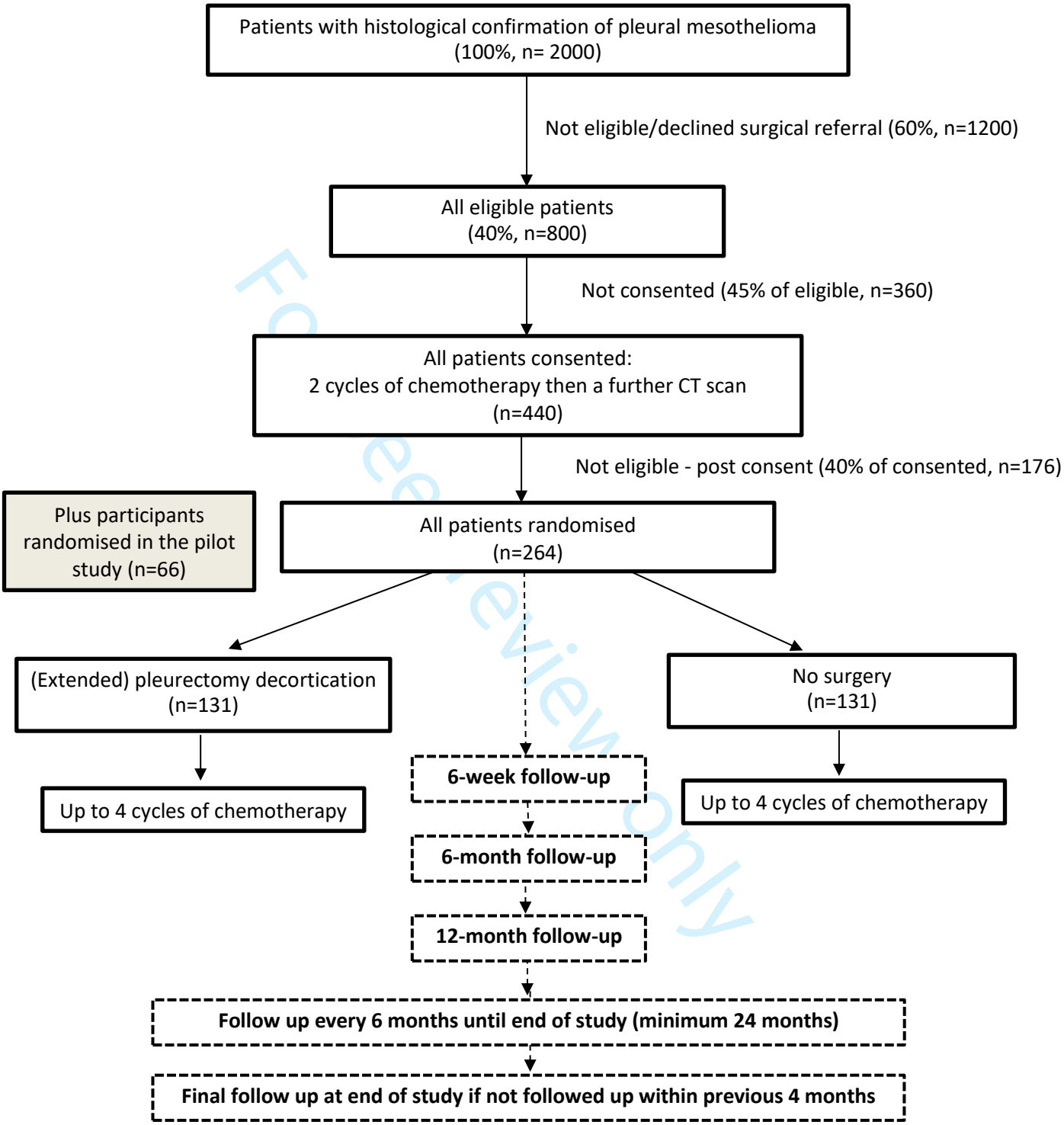
Figure 1 **Trial schema showing the recruitment pathway for the MARS 2 study**



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3,23
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6,7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7,8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8,9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8,9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7,8, 13,14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12,13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12-14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10,11,12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14-16

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14,15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15,16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	25
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23, 24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	25
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	4, 16
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	On request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.