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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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## 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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34 pleurectomy decortication; cancer

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## 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 7<sup>th</sup> 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,<sup>1</sup> 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.<sup>2</sup> 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)<sup>3</sup>, has been associated with only an additional 3 months of survival.<sup>4</sup> As the median survival for mesothelioma patients is 12.1 months,<sup>4</sup> 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).<sup>5</sup>

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.<sup>6</sup> 'Extended' pleurectomy decortication can also be carried out, when parietal and visceral pleurectomy is undertaken to remove all gross

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3 tumour, including the resection of the diaphragm and/or pericardium. The other main types  
4 of surgery for mesothelioma are: i) extra-pleural pneumonectomy, which is defined as en  
5 bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium, and  
6 diaphragm (in cases where the pericardium and/or diaphragm are not involved by tumour,  
7 these structures may be left intact) and partial pleurectomy, which is the partial removal of  
8 parietal and/or visceral pleura for diagnostic or palliative purposes but leaving gross tumour  
9 behind.<sup>6</sup>  
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15 So far, no advantage, in terms of survival, has been observed with any type of surgery in  
16 randomised controlled trials (RCTs) conducted to date. The MARS feasibility study  
17 (ISRCTN95583524), a trial of extra-pleural pneumonectomy with adjuvant haemothorax  
18 irradiation, concluded that surgery was unlikely to offer either an improvement to survival or  
19 HRQoL and possibly harmed patients.<sup>7</sup> MesoVATS (ISRCTN34321019) concluded that  
20 partial pleurectomy did not improve survival, although it showed that patients in the better  
21 prognostic group, had improved HRQoL after 6 months.<sup>8</sup>  
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27 Suitable patients, both in the UK and internationally, are currently offered pleurectomy  
28 decortication as it is considered to carry less morbidity compared to the more extensive  
29 extra-pleural pneumonectomy but still achieves complete macroscopic resection which  
30 partial pleurectomy does not.<sup>9-11</sup> However, we do not know if pleurectomy decortication in  
31 conjunction with chemotherapy will improve survival compared to the current standard of  
32 care (chemotherapy alone). In the absence of RCTs, pleurectomy decortication may  
33 continue to be offered despite a lack of high-quality evidence of clinical efficacy or any  
34 evidence on cost-effectiveness.  
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### 41 **Aims and objectives**

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44 MARS 2 is a UK wide multicentre RCT which will test the hypothesis that (extended)  
45 pleurectomy decortication and chemotherapy is superior to chemotherapy alone with respect  
46 to overall survival for patients with pleural mesothelioma.  
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50 Specific objectives are to estimate:

- 51 A. The difference between groups in overall survival.
- 52 B. The difference between groups with respect to a range of secondary outcomes  
53 including HRQoL, progression free survival and measures of safety (adverse health  
54 events).  
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3 C. The cost effectiveness of (extended) pleurectomy decortication compared to no  
4 surgery.  
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## 7 **METHODS AND ANALYSIS**

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### 10 **Trial design**

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13 MARS 2 is a multicentre, non-blinded parallel two-group, pragmatic RCT of surgery and  
14 chemotherapy versus chemotherapy alone for suitable patients with mesothelioma.  
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17 An internal pilot funded by Cancer Research UK (award ref: C27967/A15895) and  
18 coordinated by the Papworth Trials Unit Collaboration, demonstrated the feasibility of  
19 recruitment across 14 medical sites and 2 joint medical and surgical sites of excellence, as  
20 the target of 50 participants recruited within a 24 month period was achieved.  
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23 Since the end of the pilot phase in December 2016 an additional 8 medical, 1 surgical and 2  
24 joint medical and surgical sites have been opened for the full trial. In addition, the full trial will  
25 provide recruiting sites with the support of an integrated QuinteT Recruitment Intervention  
26 (QRI)<sup>12-14</sup> to optimise recruitment and retention.  
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### 29 **Setting, centre and surgeon eligibility**

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32 This study is taking place in National Health Service (NHS) secondary care centres,  
33 including teaching and district general hospitals.  
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36 To be eligible as a medical site, the centre must:  
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42 i) be an NHS Trust with access to a multidisciplinary team (MDT) to discuss  
43 patients with mesothelioma;  
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45 ii) have a track record of treating patients with mesothelioma  
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48 To be eligible as a surgical site, the centre must:  
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52 i) be an NHS Trust with an established mesothelioma MDT;  
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54 ii) have a minimum of 2 named mesothelioma surgeons participating in the trial.  
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57 All surgeons participating in the full trial must be accredited by; i) self-reporting a minimum of  
58 5 cases in which they have performed (extended) pleurectomy decortication; ii) observing  
59 the procedure being undertaken at an established MARS 2 surgical site; iii) having a  
60 surgeon from the pilot phase observe their first MARS 2 procedure undertaken; and iv)

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3 having one randomly selected MARS 2 operation between procedures 5 and 10 observed by  
4 a surgeon from the pilot phase to ensure fidelity.  
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7 Patients from all medical (only) sites are referred to a trial-accredited surgical site for  
8 computed tomography (CT) assessment of eligibility, further discussion about the study, and  
9 surgery (if randomised to this group).  
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### 13 **Trial population**

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16 The target population are patients with a diagnosis of epithelioid, sarcomatoid or biphasic  
17 mesothelioma. Patients will be eligible to take part if ALL of the following apply:  
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- 20 • Adult aged  $\geq 16$  years of age;
- 21 • Tissue (cytology or histology) confirmed epithelioid, sarcomatoid or biphasic  
22 mesothelioma, as reviewed by MDT to be of sufficient certainty to recommend  
23 chemotherapy as treatment;
- 24 • Disease confined to one hemi-thorax based on CT assessment;
- 25 • Disease deemed surgically resectable by a surgeon at a MARS 2 surgical site;
- 26 • Deemed fit for surgery by a surgeon at a MARS 2 surgical site;
- 27 • Capacity to provide written informed consent to participate in the trial.

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30 Patients will not be eligible if they have:  
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- 34 • Severe shortness of breath (Eastern Cooperative Oncology Group (ECOG) status  $\geq$   
35 2; or pre-operative forced expiratory volume after one second (FEV1) or transfer  
36 factor of the lung for carbon monoxide (TLco) less than 20%);
- 37 • Severe heart failure (NYHA III or IV, or ejection fraction less than 30% by  
38 echocardiogram);
- 39 • End stage kidney failure requiring dialysis;
- 40 • Liver failure (e.g. encephalopathy and/or coagulation abnormalities);
- 41 • Any other serious concomitant disorder that would compromise participant safety  
42 during surgery;
- 43 • Prisoner;
- 44 • Patient lacks capacity to consent;
- 45 • Existing co-enrolment in another interventional study that aims to improve survival.

### 56 **Patient approach, consent and randomisation**

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3 The local research team at the medical site will take written informed consent from  
4 participants. In addition to the main study, the team may also seek consent for audio-  
5 recording of consultations and participation in interviews, for QRI purposes. Participants will  
6 then receive two cycles of chemotherapy (standard care) and have a further CT scan to  
7 confirm eligibility (i.e. disease still resectable) before being randomised, using a secure web-  
8 based randomisation system (Sealed Envelope <https://sealedenvelope.com>).  
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14 Participants will be randomised in a 1:1 ratio. Minimisation (with a random component) will  
15 be applied for selected baseline variables (age, performance status and cell type) that  
16 influence survival, in addition to stratification by recruiting site to ensure that the cohorts are  
17 as balanced as possible.  
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### 20 21 **Trial interventions**

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

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27 • *Pleurectomy decortication and chemotherapy*; two cycles of platinum and  
28 pemetrexed chemotherapy followed by surgery and then up to four cycles of the  
29 same chemotherapy.
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31 • *Chemotherapy alone (control intervention)*; Up to six cycles of platinum and  
32 pemetrexed chemotherapy alone (current standard of care).  
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36 The trial schema is illustrated in figure 1.  
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39 After randomisation, any changes in the choice of chemotherapy, addition of other agents or  
40 entry into therapeutic trials (e.g. immunotherapies) will be permitted for patients with  
41 progressive disease. At the time of trial design, there was no national consensus on post-  
42 operative prophylactic radiotherapy so it was decided that irradiation to thoracic procedure  
43 sites may be undertaken for MARS 2 patients. Patients in both groups can also receive  
44 further surgery, including thoracic, if it is without radical intent. The aim is to conduct a  
45 pragmatic trial whilst closely monitoring uptake of additional therapies, studies or surgeries in  
46 order to account for them in the trial analyses, if required.  
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### 52 **Primary and secondary outcomes**

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54  
55 The primary outcome is survival. All participants will be followed up to the end of the trial  
56 (minimum of two years after randomisation).  
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3 Secondary outcomes have been selected to assess the efficacy of the two approaches.  
4 Secondary outcomes are 1) progression free survival to the end of the trial (minimum of two  
5 years after randomisation); 2) serious adverse health events to two years after  
6 randomisation; 3) disease specific and generic HRQoL using the following validated  
7 questionnaires: European Organisation for Research and Treatment of Cancer Quality of  
8 Life Questionnaire (EORTC QLQ-C30) – to assess the HRQoL of cancer patients; and  
9 EuroQol EQ-5D-5L<sup>15 16</sup> – a widely used generic measure of HRQoL (both of these will be  
10 measured at baseline, pre-randomisation, and 6 weeks, 6, 12, 18 and 24 months post-  
11 randomisation) and 4) healthcare resource use to the end of the study: chemotherapy cycles  
12 and initial surgical admission (for chemotherapy plus surgery group), and further resources  
13 measured at 6 weeks post-randomisation then every 6 months, with a final follow up at the  
14 end of the study if not followed up in the previous 4 months.  
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### 23 **Data collection**

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25  
26 The schedule for data collection for the study is shown in table 1. Data will be collected onto  
27 purpose-designed case report forms (CRFs) and participant completed questionnaires and  
28 entered onto a bespoke database for data cleaning and analysis. Access to the database will  
29 be via a secure password-protected web-interface hosted on an NHS server. Data about  
30 adverse events will be collected and reported in accordance with Sponsor's and regulatory  
31 requirements.  
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**Table 1 Data collection**

	Pre-randomisation				Post-randomisation							
	Screening	Baseline	2 cycles chemotherapy	End of chemotherapy cycle 2	Surgical admission *	Up to 4 cycles chemotherapy	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.

1  
2  
3 In addition, the study's primary outcome is an objective measure (survival), and clear  
4 definitions of each secondary outcome measure will be provided to trial personnel. The  
5 HRQoL follow-up questionnaires may be more at risk of bias than other measures, but  
6 patients will not have had this surgery previously and as such, should not have any  
7 expectation regarding its effect on their HRQoL. Missing outcome data will be minimised, as  
8 survival and progression free survival data can be obtained from hospital records. Losses to  
9 follow up will be minimised by maintaining regular contact with participants (by telephone  
10 and post) to complete follow-up questionnaires. Non-adherence to randomised allocation will  
11 be documented. Bias in the reported results will be minimised by having pre-specified  
12 outcomes in the trial protocol and a pre-specified analysis plan.  
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### 20 **Sample size**

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23 The total sample size has been set at 328 participants (164 per group). The patients  
24 randomised in the pilot trial will contribute to the total sample size. The study will have 80%  
25 power to detect a hazard ratio (HR) of 0.7 at 5% statistical significance (2-sided), modelled  
26 on a published assumption of a median survival time of 16.8 months in mesothelioma  
27 patients who were fit enough to receive surgery, but did not have it<sup>17</sup> and allowing for 10%  
28 cross-over from the medical to surgery groups (as noted in previous trials such as MARS  
29 17). Cross-over will be minimised through instruction (i.e. recruit only patients who have  
30 equipoise from the outset) and education.  
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36  
37 The relative difference of 30% (HR 0.7) was regarded as the minimally important difference  
38 for patients and clinicians to choose surgery given the risks of the procedure. The figure was  
39 chosen by the trial's patient and public involvement (PPI) group. The possibility that survival  
40 could be worse with surgery was also discussed, and a relative difference of 30% also  
41 regarded as an appropriate difference to indicate harm, therefore a two-tailed test for  
42 superiority was agreed.  
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### 47 **Patient and Public Involvement**

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49  
50 Patient and public representatives were involved from inception and advised on the trial  
51 design of MARS 2, the identification of the choice of the primary outcome and defined the  
52 minimally important difference in relative survival.  
53  
54  
55

56  
57 The study team have continuing engagement with the Royal Brompton Hospital Cancer  
58 Consortia PPI group that consists of patients and carers who have undergone surgery for  
59 lung cancer and mesothelioma to advise on patient orientated questions that arise from the  
60



1  
2  
3 trial conduct. One patient from the PPI group, a mesothelioma survivor, has agreed to sit on  
4 the Trial Steering Committee. The PPI group will also be involved in the dissemination of  
5 study results.  
6  
7

### 8 9 **Integrated QuinteT Recruitment Intervention (QRI)**

10  
11 Recruitment to RCTs can be challenging<sup>18</sup>, particularly for surgical trials.<sup>19</sup> An integrated QRI  
12 will therefore be employed during the main study phase to optimise recruitment and  
13 retention. The aim of the QRI is to understand the recruitment process and how it operates  
14 in clinical centres, so that sources of recruitment difficulties can be identified, and  
15 suggestions made to change aspects of design, conduct, organisation or training.  
16  
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20  
21 A multi-faceted, flexible approach will be used to investigate site-specific or wider  
22 recruitment obstacles. These will comprise the following:  
23

- 24  
25 - Mapping of eligibility and recruitment pathways to collate basic data about the levels  
26 of eligibility and recruitment, and identify points at which patients opt in or out of the  
27 trial;  
28
- 29 - In-depth, semi-structured interviews with a purposive sample of staff members  
30 involved with aspects of trial design/management and recruitment across centres,  
31 and patients eligible for recruitment to the trial. Interviews will explore participants'  
32 perspectives of the trial, views on the presentation of study information,  
33 understanding of trial processes (e.g. randomisation), and reasons underlying  
34 decisions to accept or decline the trial. In addition, interviews with staff and other  
35 individuals involved in the trial will explore perspectives on the trial design and  
36 protocol; views about the evidence on which the trial is based; perceptions of  
37 uncertainty/equipoise for themselves and their colleagues; methods for identifying  
38 eligible patients; views on eligibility, and examples of actual recruitment successes  
39 and difficulties. Interview topic guides will be used to ensure similar topic areas are  
40 covered across interviews, while still providing the scope for participants to raise  
41 issues of pertinence to them.  
42
- 43 - Audio recording of consultations between healthcare staff and potentially eligible  
44 patients across centres to understand the recruitment process at each centre and to  
45 identify and investigate the challenges to recruitment. The QRI researcher will listen  
46 to and qualitatively analyse the appointments, documenting instances such as  
47 unclear, insufficient or imbalanced information provision and unintentional  
48 transferring of clinician treatment preferences to patients.  
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- 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.

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3 Two subgroup analyses are planned: i) comparing primary and secondary outcomes by the  
4 experience level of the surgical site; and ii) comparing the primary outcome by type of  
5 mesothelioma (epithelioid, sarcomatoid or biphasic). An exploratory analysis investigating  
6 the effect of surgeon (surgical group only) will be performed for the primary outcome.  
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10 No interim analyses are planned. The primary analysis will take place when follow-up is  
11 complete for all recruited participants.  
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### 14 **Economic evaluation**

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17 The economic evaluation will compare the costs and effects of surgery versus no surgery,  
18 following established guidelines as set out by NICE.<sup>20</sup> The within-trial cost-effectiveness  
19 analysis will be undertaken from an NHS and personal social services perspective, with a  
20 time horizon from time of consent to 24 months post-randomisation. The primary outcome  
21 measure for the economic evaluation will be quality adjusted life years (QALYs), estimated  
22 using the EuroQol EQ-5D-5L at each follow up timepoint.<sup>15 16</sup> Resource use data collection  
23 will be integrated into the trial CRFs for chemotherapy cycles and surgery (if applicable, this  
24 will include details of the surgical procedure, length of stay in hospital by level of care, and  
25 post-operative complications) and be collected at each follow up timepoint.  
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33 Unit costs will be sought to value resource use data, and the total costs per participant  
34 calculated. Responses to the EQ-5D-5L will be assigned valuations according to NICE  
35 guidance at the time of analysis,<sup>21</sup> and combined with survival to calculate QALYs gained  
36 per participant. Missing resource use and EQ-5D-5L data will be handled using multiple  
37 imputation methods.<sup>22</sup> From the average costs and QALYs gained in each trial group, the  
38 incremental cost-effectiveness ratio will be derived, producing an incremental cost per QALY  
39 gained of surgery compared to no surgery. Sensitivity analyses will assess the impact of  
40 varying key parameters on baseline cost-effectiveness results. Results will be expressed in  
41 terms of a cost-effectiveness acceptability curve, which indicates the likelihood that surgery  
42 is cost-effective for different levels of willingness to pay for health gain.  
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### 50 **Ethics and dissemination**

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52 The study intervention is already routinely used in the NHS. This study has been reviewed  
53 and given favourable opinion by the London - Camberwell St. Giles Research Ethics  
54 Committee (REC; reference 13/LO/1481) on 7th November 2013. The pilot study was  
55 managed by Papworth Trials Unit Collaboration and the main trial is managed by the Bristol  
56 Trials Centre Clinical Trials and Evaluation Unit and sponsored by Royal Brompton &  
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1  
2  
3 Harefield NHS Foundation Trust. Each participant has the right to withdraw at any time. In  
4 addition, the investigator may withdraw the participant from their allocated treatment group if  
5 a clinical reason for not performing the surgical intervention is discovered. If a participant  
6 wishes to withdraw, any data already collected will be included in the study analyses, unless  
7 the participant expresses a wish for their data to be excluded. Withdrawing patients will be  
8 asked if they would continue in follow up and complete the requisite questionnaires.  
9  
10 Participants who choose to withdraw from the study will be treated according to their  
11 hospitals' standard procedures.  
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17 The findings will be disseminated by usual academic channels, i.e. presentation at  
18 international meetings and peer-reviewed publications. A full report for the funder will be  
19 written on completion of the study and a lay summary of the results provided to patients.  
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### 23 **Major changes to protocol**

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25 Since the first study protocol was approved by the REC (the current version is v6.0, 10 April  
26 2019), the following changes have been made:  
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- 30 • Qualitative assessment sub-study added, as part of the pilot phase only.
- 31 • The EuroQol EQ-5D-5L was added.
- 32 • Updates to transition from pilot phase to main study, including addition of the  
33 integrated QRI and economic evaluation, and removal of the collection of blood and  
34 tissue samples, and one of the disease specific questionnaires – the EORTC QLQ  
35 LC-13.
- 36 • Length of follow up extended from two years until the end of the study for all  
37 participants to ensure that the study has 80% power.
- 38 • Video-recording aspect of the surgical quality assurance removed as this was  
39 deemed impractical by sites, and it was agreed that it was unnecessary by the Data  
40 Safety and Monitoring Committee and the Trial Steering Committee, acknowledging  
41 the other surgical quality assurance measures that are in place.  
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50 The relevant regulatory approvals were obtained for amendments to the protocol. Relevant  
51 parties (eg, investigators, trial participants) were informed.  
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### 55 **Study progress**

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3 Recruitment started in May 2015 and 304 patients have been randomised so far (correct on  
4 25 March 2020). 66 patients from the pilot study are included in this figure. Recruitment will  
5 continue until 1<sup>st</sup> June 2020.  
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9 The full protocol is available from:

10 <https://www.journalslibrary.nihr.ac.uk/programmes/hta/1518831/>  
11  
12

### 13 **ADDITIONAL FIGURES**

14  
15 **Figure 1.** Trial schema showing the recruitment pathway for the MARS 2 study  
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### 20 **ABBREVIATIONS**

21  
22  
23 CONSORT- Consolidated Standards of Reporting Trials  
24 CRF – Case Report Form  
25 CT- computed tomography  
26 ECOG- Eastern Cooperative Oncology Group  
27 EORTC- European Organisation for Research and Treatment of Cancer  
28 FEV1- forced expiratory volume after one second  
29 HR- hazard ratio  
30 HRQoL- health related quality of life  
31 ISRCTN - International Standard Randomised Controlled Trials Number  
32 MDT – multidisciplinary team  
33 NHS- National Health Service  
34 NICE- National Institute for Health and Care Excellence  
35 NIHR- National Institute for Health Research  
36 NYHA – New York Heart Association  
37 PPI- patient and public involvement  
38 QALY- quality adjusted life years  
39 QLQ- quality of life questionnaire  
40 QuinteT – Qualitative research integrated within trials  
41 QRI- QuinteT Recruitment Intervention  
42 RCT- randomised controlled trial  
43 REC- Research Ethics Committee  
44 TLco- transfer factor of the lung for carbon monoxide  
45 TMG – Trial Management Group  
46 UK- United Kingdom  
47  
48

### 49 **Acknowledgements**

50 The MARS 2 trial is sponsored by The Royal Brompton and Harefield NHS Foundation  
51 Trust. The sponsor will be responsible for the oversight of the MARS 2 study and to ensure  
52 the trial is managed appropriately. We want to thank the large teams at each hospital who  
53 work on the MARS 2 study (representatives from each are listed below). We would also like  
54 to thank Dr Fiona McDonald from the Royal Marsden Hospital, Dr Nagmi Qureshi from  
55 Papworth Hospital and Professor Simon Padley from the Royal Brompton Hospital for their  
56 radiotherapy advisory roles. Thank you also to Professor Andrew Nicholson for his  
57 histopathology advisory role for MARS 2.  
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60

1  
2  
3 **Collaborators**

4 **\*MARS 2 Trialists**

5 **Project management team members:**

6 Professor Eric Lim, Chief Investigator  
7 Professor Chris Rogers, Methodological Lead and Statistician  
8 Kate Ashton, Clinical Trial Coordinator  
9 Athanasia Gravani, Clinical Trial Coordinator  
10 Holly McKeon, Clinical Trial Coordinator  
11 Wendy Underwood, Clinical Trial Coordinator  
12 Dr Barbara Warnes, Clinical Trial Coordinator  
13 Katherine Joyce, Assistant Clinical Trial Coordinator  
14 Rachel Brophy, Assistant Clinical Trial Coordinator  
15 Rosie Harris, Medical Statistician  
16 Dr Nicola Mills, Senior Research Fellow, Quintet Research Intervention  
17 Dr Daisy Elliott, Research Fellow, Quintet Research Intervention  
18 Nicola Farrar, PhD Student, Quintet Research Intervention  
19 Dr Elizabeth Stokes, Health Economist

20  
21  
22  
23  
24  
25 **Papworth Trials Unit Collaboration (pilot study):**

26 Robert Rintoul, Director of Papworth Trials Unit Collaboration and Honorary Consultant  
27 Respiratory Physician  
28 Victoria Hughes, Senior R&D Manager  
29 Jane Elliott, Clinical Project Manager  
30 Claire Matthews, Trial Manager  
31 Philip Noyes, Trial Administrator

32  
33  
34  
35 **Participating Sites Members: pilot study and main trial**

36 ***University Hospitals of Leicester NHS Trust – medical and surgical site (opened***  
37 ***22/04/2015)***

38 Dean Fennell, Principal Investigator, Chair of Thoracic Medical Oncology  
39 Apostolos Nakas, Consultant Thoracic Surgeon  
40 Louise Nelson, Research Nurse

41  
42 ***Sheffield Teaching Hospitals NHS Foundation Trust – medical and surgical site (opened***  
43 ***13/05/2015)***

44 John Edwards, Principal Investigator, Consultant Thoracic Surgeon  
45 Sara Tenconi, Consultant Thoracic Surgeon  
46 Laura Soggi, Consultant Thoracic Surgeon  
47 Hilary Wood, Data Manager  
48 Helena Hanratty, Research Nurse

49 Helena Stanley, Mesothelioma UK Clinical Nurse Specialist

50  
51  
52 ***South Tyneside and Sunderland NHS Foundation Trust – medical site (opened***  
53 ***19/06/2015)***

54 Liz Fuller, Principal Investigator, Consultant Respiratory Physician  
55 Judith Moore, Clinical Trials Officer

56 ***Papworth Hospital NHS Foundation Trust – medical site (opened 01/07/2015)***

57 Robert Rintoul, Principal Investigator, Honorary Consultant Respiratory Physician  
58 Suzanne Miller, Clinical Trials Coordinator  
59 Amy Gladwell, Clinical Trials Administrator  
60

1  
2  
3 Jenny Castedo, Research Nurse

4 Amanda Stone, Senior Research Nurse

5 **Colchester Hospital University NHS Foundation Trust – medical site (opened**  
6 **03/11/2015)**

7  
8 Dakshinamoorthy Muthukumar, Principal Investigator, Consultant Oncologist

9 Charlotte Ingle, Co-Investigator, Consultant Clinical Oncologist

10 Hayley Hewer, Research Nurse

11 **South Tees Hospitals NHS Foundation Trust – medical site (opened 16/11/2015)**

12 Talal Mansy, Principal Investigator, Consultant Medical Oncologist

13 Louise Li, Co-Investigator, Consultant Medical Oncologist

14 Eleanor Aynsley, Co-Investigator, Consultant Clinical Oncologist

15 Andrea Watson, Clinical Trials Coordinator

16 Charlotte Jacobs, Clinical Trials Coordinator

17 **The Clatterbridge Cancer Centre NHS Foundation Trust – medical site (opened**  
18 **25/11/2015)**

19 Tony Pope, Principal Investigator, Consultant in Clinical Oncology

20 Alison Hassall, Research Nurse

21 Masuma Begum, Clinical Trials Assistant

22 **University Hospitals of Derby and Burton NHS Foundation Trust – medical site,**  
23 **(opened 26/11/2015)**

24 Manjusha Keni, Principal Investigator, Consultant Clinical Oncologist

25 Christopher Worth, Cancer Clinical Research Nurse Lead

26 Ellie Piggott, Research Practitioner

27 Elizabeth Nadin, Research Practitioner

28 **Leeds Teaching Hospitals NHS Trust – medical site (opened 02/12/2015)**

29 Richard Milton, Principal Investigator, Consultant Thoracic Surgeon

30 Victoria Ashford-Turner, Research Nurse

31 Matthew Callister, Respiratory Consultant

32 **Manchester University NHS Foundation Trust – medical site (opened 21/12/2015)**

33 Paul Taylor, Principal Investigator

34 Yvonne Summers, Sub Investigator

35 Raffaele Califano, Sub Investigator

36 Laura Cove-Smith, Sub Investigator

37 Matt Evison, Sub Investigator

38 Maria Blinston, Research Nurse

39 Sara Waplinton, Clinical Trials Coordinator

40 Amal Ismail, Clinical Trials Administrator

41 Rachel Chant, Research Nurse

42 Asmita Desai, Research Nurse

43 Juliette Novasio, Clinical Trials Manager

44 Marie Kirwan, Research Nurse

45 **The Royal Wolverhampton NHS Trust – medical site (opened 04/01/2016)**

46 Pek Koh, Principal Investigator, Consultant Clinical Oncologist

47 Ian Morgan, previous Principal Investigator, Consultant Cardiothoracic Surgeon

48 Victoria Lake, Research Nurse

49 Nichola Harris, Research Nurse

50 **Royal Gwent Hospital, Aneurin Bevan University Health Board – medical site (opened**  
51 **08/02/2016)**

1  
2  
3 Andreea Alina Ionescu, Principal Investigator, Consultant Respiratory Physician  
4 Simon Hodge, Research Nurse

5 ***The Royal Marsden NHS Foundation Trust – medical site (opened 08/04/2016)***

6 Prof Sanjay Popat, Principal Investigator, Consultant Medical Oncologist

7 Chelsea sub-site

8 Dr Nadia Yousaf, Sub-Investigator

9 Dr Nadza Tokaca, Sub-Investigator

10 Dr Adam Januszewski, Sub-Investigator

11 Dr Avani Athauda, Sub-Investigator

12 Dr Anisha Ramessur, Sub-Investigator

13 Dr Emily Grist, Sub-Investigator

14 Dr Niamh Colman, Sub-Investigator

15 Dr Michael Flynn, Sub-Investigator

16 Joan Joyce, Research Nurse

17 Sarah Vaughan, Research Nurse

18 Maria Piga, Senior Research Nurse

19 Derya Sahin, Senior Research Nurse

20 Agnieszka Yongue, Senior Trials Coordinator

21 Emma Turay, Clinical Trials Administrator

22 Sutton sub-site

23 Prof Mary O'Brien, Sub-Investigator

24 Dr Jaishree Bhosle, Sub-Investigator

25 Dr Rajiv Kumar, Sub-Investigator

26 Dr Charlotte Milner-Watts, Sub-Investigator

27 Dr Jessica Brown, Sub-Investigator

28 Dr David Walder, Sub-Investigator

29 Dr Alexandros Georgiou, Sub-Investigator

30 Dr Xiaorong Wu, Sub-Investigator

31 Dr Naila Kaudeer, Sub-Investigator

32 Dr Kroopa Joshi, Sub-Investigator

33 Dr Michael Davidson, Sub-Investigator

34 Dr Shelize Khakoo, Sub-Investigator

35 Bee Ayite, Research Nurse

36 Kathryn Priest, Research Nurse

37 James Dobbyn, Senior Research Nurse

38 Vasanthi Prathapan, Senior Research Nurse

39 Deborah McCrimmon, Research Radiographer

40 Natalie Ash, Assistant Practitioner

41 Alison Norton, Senior Clinical Trial Coordinator

42 Bianca Peet, Senior Trials Manager

43 Libby Hennessy, Clinical Trials Administrator

44 Rosemary Johnson, Clinical Trials Administrator

45 Laura White, Clinical Trials Administrator

46 Kingston sub-site

47 Dr Edward Armstrong, Sub-Investigator

48 Dr Maria Coakley, Sub-Investigator

49 Dr Scott Shepherd, Sub-Investigator

50 Dr Narda Chaabouni, Sub-Investigator



1  
2  
3 Dr Katherina Sreter, Sub-Investigator  
4 Dr Vasileios Angelis, Sub-Investigator  
5 Dr Mariko Morishita, Sub-Investigator  
6 Dr Jose Roca, Sub-Investigator

7  
8 Mary Jane de los Reyes Lauigan, Research Nurse  
9 Katrin Sainudeen, Clinical Trials Practitioner  
10 Helen Morgan, Clinical Trials Administrator

11 ***Peterborough City Hospital, North West Anglia NHS Foundation Trust – medical site***  
12 ***(opened 16/05/2016)***

13  
14 Dr Sarah Treece, Principal Investigator, Consultant Clinical Oncologist  
15 Dr Abigail Hollingdale, Co-Investigator, Consultant Clinical Oncologist  
16 Chloe Eddings, Study Co-ordinator/Research Nurse  
17 Holly Warman, Study Co-ordinator/Clinical Trials Assistant

18  
19  
20 **Participating Sites Members: main trial only**

21 ***Barts Health NHS Trust – medical and surgical site (opened 05/06/2017)***

22 Kelvin Lau, Principal Investigator, Consultant Thoracic Surgeon  
23 David Waller, Consultant Thoracic Surgeon  
24 Jeremy Steele, Consultant Medical Oncologist  
25 Jo Hargrave, Mesothelioma Clinical Nurse Specialist  
26 Resmi Jayachandran, Senior Clinical Trials Practitioner  
27 Pratistha Panday, Clinical Trials Assistant

28  
29  
30 ***The Beatson West of Scotland Cancer Centre, Greater Glasgow Health Board –***  
31 ***medical site (opened 14/07/2017)***

32 Clinton Ali, Principal Investigator, Consultant Medical Oncologist  
33 Austin McInnes, Clinical Trial Coordinator

34  
35 ***Golden Jubilee National Hospital – surgical site (opened 14/07/2017)***

36 Alan Kirk, Principal Investigator, Consultant Thoracic Surgeon  
37 Rocco Bilancia, Consultant Thoracic Surgeon  
38 Julie Buckley, Research Nurse  
39 Elizabeth Boyd, Research Nurse

40  
41 ***North Bristol NHS Trust – medical site (opened 28/02/2018)***

42 Nick Maskell, Principal Investigator, Consultant in Respiratory Medicine  
43 Natalie Zahan-Evans, Research Nurse  
44 Anna Morley, Senior Research Nurse

45  
46 ***Norfolk and Norwich University Hospitals NHS Foundation Trust – medical site (opened***  
47 ***12/06/2018)***

48 Zacharias Tasigiannopoulos, Principal Investigator, Consultant Clinical Oncologist  
49 Adela Dann, Clinical Trials Practitioner  
50 Eleanor Mishra, Consultant Respiratory Physician  
51 Pinelopi Gkogkou, Consultant Clinical Oncologist

52  
53 ***University Hospitals Plymouth NHS Trust – medical site (opened 16/07/2018)***

54 Amy Roy, Principal Investigator, Consultant Clinical Oncologist  
55 Irene Harvey, Research Nurse  
56 Hilary Congdon, Research Nurse

57  
58 ***Barking, Havering and Redbridge University Hospitals NHS Trust – medical site***  
59 ***(opened 24/07/2018)***

60 Jonathan Shamash, Principal Investigator, Consultant Medical Oncologist

1  
2  
3 Alison Ray, Clinical Trials Nurse

4 ***Guy's and St. Thomas' NHS Foundation Trust – medical and surgical site (opened***  
5 ***10/08/2018)***

7 Andrea Bille, Principal Investigator, Consultant Thoracic Surgeon

8 Jehan Mansi, Clinical Trials Practitioner

9 Amy Quinn, Clinical Research Nurse

10 ***Oxford University Hospitals NHS Foundation Trust – medical site (opened 19/10/2018)***

11 Najib M Rahman, Principal Investigator, Consultant and Senior Lecturer in Respiratory  
12 Medicine

14 Jack Seymour, Research Nurse

15 Hannah Ball, Mesothelioma Nurse

16 Meenali Chitnis, Consultant Clinical Oncologist

17 ***Maidstone and Tunbridge Wells NHS Trust – medical site (opened 19/10/2018)***

18 Riyaz Shah, Principal Investigator, Consultant Medical Oncologist

20 Eirini Petroyannou, Research Nurse

21 Kimberley Snoad, Clinical Trials Administrator

22 Monica Tavares Barbosa, Research Nurse

23 ***University Hospitals Birmingham NHS Foundation Trust – medical site (opened***  
24 ***03/01/2019)***

26 Professor Gary Middleton, Principal Investigator, Professor in Medical Oncology

27 Philip Earwaker, Consultant Medical Oncologist

28 Haider Abbas, Consultant Medical Oncologist

30 Parminder Sohal, Oncology Research Sister

### 31 32 **Independent Trial Steering Committee members**

33 Prof Marcus Flather MBBS FRCP (Chair), Clinical Professor in Medicine; Dr Paul Beckett,  
34 Consultant Respiratory Physician; Miss Carol Tan, Consultant Thoracic Surgeon - has  
35 declared the following competing interest: ethicon endostaplers – consultancies; Prof Fergus  
36 Gleeson FRCP FRCR, Professor of Radiology and Consultant Radiologist; Prof Fergus  
37 MacBeth, Consultant Oncologist; Hon Dr Mavis Nye, Patient Advocate; Dr Harvey Pass,  
38 Professor of Thoracic Oncology; Dr Pauline Leonard, Consultant Medical Oncologist – has  
39 declared the following competing interests: Teva, Amgen, LCO Pharma; Prof Tom Treasure  
40 MS MD FRCS FRCP, Clinical Operations Research Unit.

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

### 44 45 **Independent Data Monitoring and Safety Committee members**

46 Prof Linda Sharples (Chair), Professor of Medical Statistics; Prof Valerie Rusch, Consultant  
47 Thoracic Surgeon; Prof Mark Britton, Consultant Physician; Dr Robin Rudd, London Lung  
48 Cancer Group; Prof Joseph S. Friedberg MD FACS, Professor of Surgery and Surgeon-in-  
49 Chief; Prof Peter Goldstraw, Emeritus Professor of Thoracic Surgery.

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

### 52 53 **Contributors**

54 EL - Study design, preparation and drafting of protocol and manuscript, Chief Investigator for  
55 the trial; LD - Study design, preparation of protocol and review of manuscript; JGE - Study  
56 design, preparation of protocol and review of manuscript, Principal Investigator and acquired  
57 data for the study; DE - Design of integrated qualitative study, preparation of study protocol,  
58 review of manuscript; DAF - Study design, preparation of protocol and review of manuscript,  
59  
60

Principal Investigator and acquired data for the study; SP - Study design, preparation of protocol and review of manuscript, Principal Investigator and acquired data for the study; RR - Study design, preparation of protocol and review of manuscript, Principal Investigator and acquired data for the study; DW - Study design, preparation of protocol and review of manuscript, acquired data for the study; CA - Review of manuscript, Principal Investigator and acquired data for the study; AB - Review of manuscript, Principal Investigator and acquired data for the study; LF - Review of manuscript, Principal Investigator and acquired data for the study; AAI - Review of manuscript, Principal Investigator and acquired data for the study; MK - Review of manuscript, Principal Investigator and acquired data for the study; AK - Review of manuscript, Principal Investigator and acquired data for the study; PK - Review of manuscript, Principal Investigator and acquired data for the study; KL - Review of manuscript, Principal Investigator and acquired data for the study; TM - Review of manuscript, Principal Investigator and acquired data for the study; NAM - Review of manuscript, Principal Investigator and acquired data for the study; RM - Review of manuscript, Principal Investigator and acquired data for the study; DM - Review of manuscript, Principal Investigator and acquired data for the study; TP- Review of manuscript, Principal Investigator and acquired data for the study; AR - Review of manuscript, Principal Investigator and acquired data for the study; RS - Review of manuscript, Principal Investigator and acquired data for the study; JS - Review of manuscript, Principal Investigator and acquired data for the study; ZT - Review of manuscript, Principal Investigator and acquired data for the study; PT - Review of manuscript, Principal Investigator and acquired data for the study; ST - Review of manuscript, Principal Investigator and acquired data for the study; KA - Study design, preparation and drafting of protocol and manuscript, oversight study conduct and acquisition of data; RAH - Statistical analysis plan, review of manuscript; KJ - Preparation and drafting of manuscript, oversight study conduct and acquisition of data; BW- Drafting of manuscript, oversight study conduct and acquisition of data; NM - Conduct of integrated qualitative study, preparation of study protocol, review of manuscript; ES - Design of health economic component, preparation of study protocol, review of manuscript; CAR - Study design, sample size and statistical analysis plan, drafting of protocol, review of manuscript.

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## 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 Novartis, personal fees from Covidien, personal fees from Roche, personal fees from Lilly 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 AstraZeneca (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 Boehringer 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

1  
2  
3 This study received a favourable opinion by the London - Camberwell St. Giles Research  
4 Ethics Committee (REC; reference 13/LO/1481) on 7th November 2013.  
5  
6

### 7 **Provenance and peer review**

8 Not commissioned, externally peer reviewed.  
9

### 10 **Data sharing**

11 Data will not be made available for sharing until after publication of the main results of the  
12 study. Thereafter, anonymised individual patient data will be made available for secondary  
13 research, conditional on prior consent having been given by the patients and assurance from  
14 the secondary researcher that the proposed use of the data is compliant with the Medical  
15 Research Council (MRC) Policy on Data Sharing regarding scientific quality, ethical  
16 requirements and value for money. A minimum requirement with respect to scientific quality  
17 will be a publicly available pre-specified protocol describing the purpose, methods and  
18 analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The  
19 second file containing patient identifiers would be retained for record linkage or a similar  
20 purpose, Subject to confirmation that the secondary research protocol has been approved by  
21 a UK REC or other similar, approved ethics review body.  
22  
23  
24  
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28 Joyce: 0000-0002-5539-7178; Chris A Rogers: 0000-0002-9624-2615  
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31

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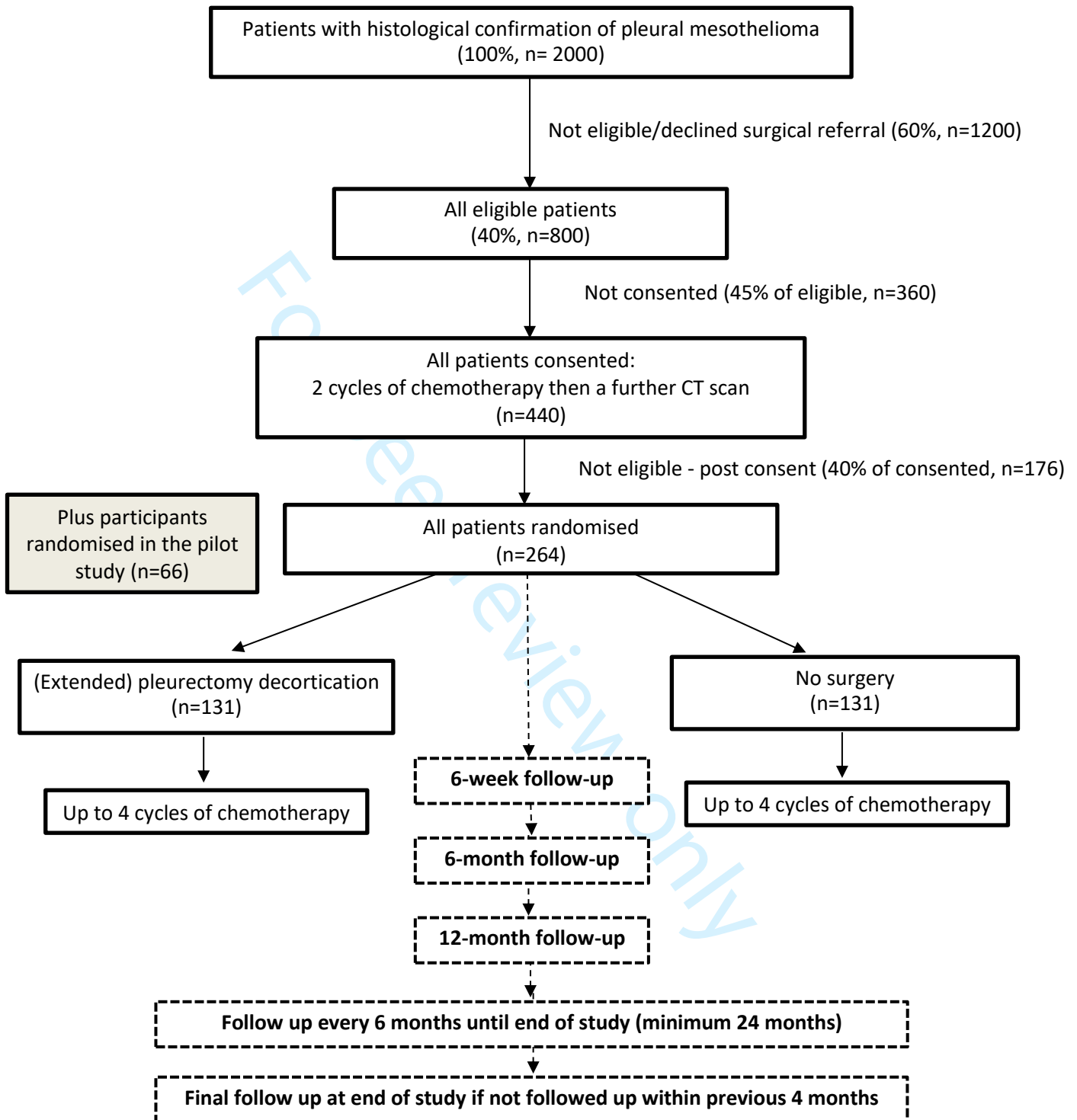
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**Figure 1** Trial schema showing the recruitment pathway for the MARS 2 study







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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
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

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant 5,6  
4 rationale 6a studies (published and unpublished) examining benefits and harms for each intervention  
5

6 6b Explanation for choice of comparators 6  
7

8 Objectives 7 Specific objectives or hypotheses 6,7  
9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), 7  
11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)  
12  
13

14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will 7,8  
17 be collected. Reference to where list of study sites can be obtained  
18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and 8  
20 individuals who will perform the interventions (eg, surgeons, psychotherapists)  
21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be 8,9  
23 administered  
24

25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose 8,9  
26 change in response to harms, participant request, or improving/worsening disease)  
27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence 7,8, 13,14  
29 (eg, drug tablet return, laboratory tests)  
30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial 9  
32

33 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood 9-11  
34 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,  
35 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen  
36 efficacy and harm outcomes is strongly recommended  
37

38 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for 11  
39 participants. A schematic diagram is highly recommended (see Figure)  
40  
41  
42

1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including 12,13  
 2 clinical and statistical assumptions supporting any sample size calculations  
 3

4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 12-14  
 5  
 6

7 **Methods: Assignment of interventions (for controlled trials)**

8 Allocation:  
 9

10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any 9  
 11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction  
 12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants  
 13 or assign interventions  
 14  
 15

16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, 9  
 17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  
 18 mechanism  
 19  
 20

21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to 9  
 22 interventions  
 23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome 11  
 25 assessors, data analysts), and how  
 26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's N/A  
 28 allocated intervention during the trial  
 29  
 30

31 **Methods: Data collection, management, and analysis**

32  
 33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related 10,11,12  
 34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of  
 35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.  
 36 Reference to where data collection forms can be found, if not in the protocol  
 37  
 38

39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be 14-16  
 40 collected for participants who discontinue or deviate from intervention protocols  
 41  
 42

1	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
2				
3				
4				
5	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
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
9				
10		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
11				
12				
13				
14	<b>Methods: Monitoring</b>			
15				
16	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
17				
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21				
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
23				
24				
25	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
26				
27				
28	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
29				
30				
31				
32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15,16
35				
36				
37	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
38				
39				
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41				
42				

1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
5				
6				
7	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
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23, 24
11				
12				
13	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
14				
15				
16				
17	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
18				
19				
20	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
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	On request
32				
33				
34	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
35				
36				

\*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. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# 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:	<i>BMJ Open</i>
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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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## 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 7<sup>th</sup> 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,<sup>1</sup> 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.<sup>2</sup> 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)<sup>3</sup>, has been associated with only an additional 3 months of survival.<sup>4</sup> As the median survival for mesothelioma patients is 12.1 months,<sup>4</sup> 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).<sup>5</sup>

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.<sup>6</sup> Extended pleurectomy decortication can also be carried out, when parietal and visceral pleurectomy is undertaken to remove all gross

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3 tumour, including the resection of the diaphragm and/or pericardium. In the document we  
4 use the term (extended) pleurectomy decortication to refer to either of the two procedures.  
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6 The other main types of surgery for mesothelioma are: extra-pleural pneumonectomy, which  
7 is defined as en bloc resection of the parietal and visceral pleura with the ipsilateral lung,  
8 pericardium, and diaphragm (in cases where the pericardium and/or diaphragm are not  
9 involved by tumour, these structures may be left intact) and partial pleurectomy, which is the  
10 partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes but  
11 leaving gross tumour behind.<sup>6</sup>  
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17 So far, no advantage, in terms of survival, has been observed with any type of surgery in  
18 randomised controlled trials (RCTs) conducted to date. The MARS feasibility study  
19 (ISRCTN95583524), a trial of extra-pleural pneumonectomy with adjuvant haemothorax  
20 irradiation, concluded that surgery was unlikely to offer either an improvement to survival or  
21 HRQoL and possibly harmed patients.<sup>7</sup> MesoVATS (ISRCTN34321019) concluded that  
22 partial pleurectomy did not improve survival, although it showed that patients in the better  
23 prognostic group, had improved HRQoL after 6 months.<sup>8</sup>  
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29 Suitable patients, both in the UK and internationally, are currently offered pleurectomy  
30 decortication as it is considered to carry less morbidity compared to the more extensive  
31 extra-pleural pneumonectomy but still achieves complete macroscopic resection which  
32 partial pleurectomy does not.<sup>9-11</sup> However, we do not know if (extended) pleurectomy  
33 decortication in conjunction with chemotherapy will improve survival compared to the current  
34 standard of care (chemotherapy alone). In the absence of RCTs, (extended) pleurectomy  
35 decortication may continue to be offered despite a lack of high-quality evidence of clinical  
36 efficacy or any evidence on cost-effectiveness.  
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### 43 **Aims and objectives**

44  
45 MARS 2 is a UK wide multicentre RCT which will test the hypothesis that (extended)  
46 pleurectomy decortication and chemotherapy is superior to chemotherapy alone with respect  
47 to overall survival for patients with pleural mesothelioma.  
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51 Specific objectives are to estimate:

- 52 A. The difference between groups in overall survival.
- 53 B. The difference between groups with respect to a range of secondary outcomes  
54 including HRQoL, progression free survival and measures of safety (adverse health  
55 events).  
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3 C. The cost effectiveness of (extended) pleurectomy decortication compared to no  
4 surgery.  
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## 7 **METHODS AND ANALYSIS**

### 8 **Trial design**

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12 MARS 2 is a multicentre, non-blinded parallel two-group, pragmatic RCT of surgery and  
13 chemotherapy versus chemotherapy alone for suitable patients with mesothelioma.  
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17 An internal pilot funded by Cancer Research UK (award ref: C27967/A15895) and  
18 coordinated by the Papworth Trials Unit Collaboration, demonstrated the feasibility of  
19 recruitment across 14 medical sites and 2 joint medical and surgical sites of excellence, as  
20 the target of 50 participants recruited within a 24 month period was achieved.  
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23  
24 Since the end of the pilot phase in December 2016 an additional 8 medical, 1 surgical and 2  
25 joint medical and surgical sites have been opened for the full trial. In addition, the full trial will  
26 provide recruiting sites with the support of an integrated QuinteT Recruitment Intervention  
27 (QRI)<sup>12-14</sup> to optimise recruitment and retention.  
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### 30 **Setting, centre and surgeon eligibility**

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32 This study is taking place in National Health Service (NHS) secondary care centres,  
33 including teaching and district general hospitals.  
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37 To be eligible as a medical site, the centre must:  
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42 i) be an NHS Trust with access to a multidisciplinary team (MDT) to discuss  
43 patients with mesothelioma;  
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45 ii) have a track record of treating patients with mesothelioma  
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49 To be eligible as a surgical site, the centre must:  
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- 52  
53 i) be an NHS Trust with an established mesothelioma MDT;  
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55 ii) have a minimum of 2 named mesothelioma surgeons participating in the trial.  
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59 All surgeons participating in the full trial must be accredited by; i) self-reporting a minimum of  
60 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)

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3 having one randomly selected MARS 2 operation between procedures 5 and 10 observed by  
4 a surgeon from the pilot phase to ensure fidelity.  
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7 Patients from all medical (only) sites are referred to a trial-accredited surgical site for  
8 computed tomography (CT) assessment of eligibility, further discussion about the study, and  
9 surgery (if randomised to this group).  
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### 13 **Trial population**

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16 The target population are patients with a diagnosis of epithelioid, sarcomatoid or biphasic  
17 mesothelioma. Patients will be eligible to take part if ALL of the following apply:  
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- 20 • Adult aged  $\geq 16$  years of age;
- 21 • Tissue (cytology or histology) confirmed epithelioid, sarcomatoid or biphasic  
22 mesothelioma, as reviewed by MDT to be of sufficient certainty to recommend  
23 chemotherapy as treatment;
- 24 • Disease confined to one hemi-thorax based on CT assessment;
- 25 • Disease deemed surgically resectable by a surgeon at a MARS 2 surgical site;
- 26 • Deemed fit for surgery by a surgeon at a MARS 2 surgical site;
- 27 • Capacity to provide written informed consent to participate in the trial.

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30 Patients will not be eligible if they have:  
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- 34 • Severe shortness of breath (Eastern Cooperative Oncology Group (ECOG) status  $\geq$   
35 2; or pre-operative forced expiratory volume after one second (FEV1) or transfer  
36 factor of the lung for carbon monoxide (TLco) less than 20%);
- 37 • Severe heart failure (NYHA III or IV, or ejection fraction less than 30% by  
38 echocardiogram);
- 39 • End stage kidney failure requiring dialysis;
- 40 • Liver failure (e.g. encephalopathy and/or coagulation abnormalities);
- 41 • Any other serious concomitant disorder that would compromise participant safety  
42 during surgery;
- 43 • Prisoner;
- 44 • Patient lacks capacity to consent;
- 45 • Existing co-enrolment in another interventional study that aims to improve survival.

### 56 **Patient approach, consent and randomisation**

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3 The local research team at the medical site will take written informed consent from  
4 participants. In addition to the main study, the team may also seek consent for audio-  
5 recording of consultations and participation in interviews, for QRI purposes. Participants will  
6 then receive two cycles of chemotherapy (standard care) and have a further CT scan to  
7 confirm eligibility (i.e. disease still resectable) before being randomised, using a secure web-  
8 based randomisation system (Sealed Envelope <https://sealedenvelope.com>).  
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14 Participants will be randomised in a 1:1 ratio. Minimisation (with a random component) will  
15 be applied for selected baseline variables (age, performance status and cell type) that  
16 influence survival, in addition to stratification by recruiting site to ensure that the cohorts are  
17 as balanced as possible.  
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### 20 21 **Trial interventions**

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

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27 • *(Extended) pleurectomy decortication and chemotherapy*; two cycles of platinum and  
28 pemetrexed chemotherapy followed by surgery and then up to four cycles of the  
29 same chemotherapy.
- 30  
31 • *Chemotherapy alone (control intervention)*; Up to six cycles of platinum and  
32 pemetrexed chemotherapy alone (current standard of care).  
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36 The trial schema is illustrated in figure 1.  
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39 After randomisation, any changes in the choice of chemotherapy, addition of other agents or  
40 entry into therapeutic trials (e.g. immunotherapies) will be permitted for patients with  
41 progressive disease. At the time of trial design, there was no national consensus on post-  
42 operative prophylactic radiotherapy so it was decided that irradiation to thoracic procedure  
43 sites may be undertaken for MARS 2 patients. Patients in both groups can also receive  
44 further surgery, including thoracic, if it is without radical intent. The aim is to conduct a  
45 pragmatic trial whilst closely monitoring uptake of additional therapies, studies or surgeries in  
46 order to account for them in the trial analyses, if required.  
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### 52 **Primary and secondary outcomes**

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55 The primary outcome is survival, calculated from randomisation date (randomisation occurs  
56 after the first two cycles of chemotherapy). All participants will be followed up to the end of  
57 the trial (minimum of two years after randomisation).  
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3 Secondary outcomes have been selected to assess the efficacy of the two approaches.  
4 Secondary outcomes are 1) progression free survival to the end of the trial (minimum of two  
5 years after randomisation); 2) serious adverse health events to two years after  
6 randomisation; 3) disease specific and generic HRQoL using the following validated  
7 questionnaires: European Organisation for Research and Treatment of Cancer Quality of  
8 Life Questionnaire (EORTC QLQ-C30) – to assess the HRQoL of cancer patients; and  
9 EuroQol EQ-5D-5L<sup>15 16</sup> – a widely used generic measure of HRQoL (both of these will be  
10 measured at baseline, pre-randomisation, and 6 weeks, 6, 12, 18 and 24 months post-  
11 randomisation) and 4) healthcare resource use to the end of the study: chemotherapy cycles  
12 and initial surgical admission (for chemotherapy plus surgery group), and further resources  
13 measured at 6 weeks post-randomisation then every 6 months, with a final follow up at the  
14 end of the study if not followed up in the previous 4 months.  
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### 23 **Data collection**

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

	Pre-randomisation				Post-randomisation							
	Screening	Baseline	2 cycles chemotherapy	End of chemotherapy cycle 2	Surgical admission *	Up to 4 cycles chemotherapy	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

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2  
3 \*\* If not within previous 4 months

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

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

7 \*\*\*\*\* Including resource and health service use  
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## 12 **Risk of bias**

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14  
15 Participants and clinical personnel cannot be blinded to allocation due to the nature of the  
16 study intervention. However, standard local protocols will be followed in terms of patient  
17 care. The patient information leaflet and conversations with MARS 2 site staff will describe  
18 and balance the potential benefits and risks of both having and not having surgery.  
19 Therefore, this approach will reduce participant's expectations that one or other treatment  
20 protocol will lead to a more favourable result.  
21  
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24  
25 In addition, the study's primary outcome is an objective measure (survival), and clear  
26 definitions of each secondary outcome measure will be provided to trial personnel. The  
27 HRQoL follow-up questionnaires may be more at risk of bias than other measures, but  
28 patients will not have had this surgery previously and as such, should not have any  
29 expectation regarding its effect on their HRQoL. Missing outcome data will be minimised, as  
30 survival and progression free survival data can be obtained from hospital records. Losses to  
31 follow up will be minimised by maintaining regular contact with participants (by telephone  
32 and post) to complete follow-up questionnaires. Non-adherence to randomised allocation will  
33 be documented. Bias in the reported results will be minimised by having pre-specified  
34 outcomes in the trial protocol and a pre-specified analysis plan.  
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## 42 **Sample size**

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44  
45 The total sample size has been set at 328 participants (164 per group). The patients  
46 randomised in the pilot trial will contribute to the total sample size. The study will have 80%  
47 power to detect a hazard ratio (HR) of 0.7 at 5% statistical significance (2-sided), modelled  
48 on a published assumption of a median survival time of 16.8 months in mesothelioma  
49 patients who were fit enough to receive surgery, but did not have it<sup>17</sup> and allowing for 10%  
50 cross-over from the medical to surgery groups (as noted in previous trials such as MARS  
51 17). Cross-over will be minimised through instruction (i.e. recruit only patients who have  
52 equipoise from the outset) and education.  
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3 The relative difference of 30% (HR 0.7) was regarded as the minimally important difference  
4 for patients and clinicians to choose surgery given the risks of the procedure. The figure was  
5 chosen by the trial's patient and public involvement (PPI) group. The possibility that survival  
6 could be worse with surgery was also discussed, and a relative difference of 30% also  
7 regarded as an appropriate difference to indicate harm, therefore a two-tailed test for  
8 superiority was agreed.  
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### 13 **Patient and Public Involvement**

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16 Patient and public representatives were involved from inception and advised on the trial  
17 design of MARS 2, the identification of the choice of the primary outcome and defined the  
18 minimally important difference in relative survival.  
19  
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21

22  
23 The study team have continuing engagement with the Royal Brompton Hospital Cancer  
24 Consortia PPI group that consists of patients and carers who have undergone surgery for  
25 lung cancer and mesothelioma to advise on patient orientated questions that arise from the  
26 trial conduct. One patient from the PPI group, a mesothelioma survivor, has agreed to sit on  
27 the Trial Steering Committee. The PPI group will also be involved in the dissemination of  
28 study results.  
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### 33 **Integrated QuinteT Recruitment Intervention (QRI)**

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36 Recruitment to RCTs can be challenging<sup>18</sup>, particularly for surgical trials.<sup>19</sup> An integrated QRI  
37 will therefore be employed during the main study phase to optimise recruitment and  
38 retention. The aim of the QRI is to understand the recruitment process and how it operates  
39 in clinical centres, so that sources of recruitment difficulties can be identified, and  
40 suggestions made to change aspects of design, conduct, organisation or training.  
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45 A multi-faceted, flexible approach will be used to investigate site-specific or wider  
46 recruitment obstacles. These will comprise the following:  
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48

- 49 - Mapping of eligibility and recruitment pathways to collate basic data about the levels  
50 of eligibility and recruitment, and identify points at which patients opt in or out of the  
51 trial;  
52
- 53 - In-depth, semi-structured interviews with a purposive sample of staff members  
54 involved with aspects of trial design/management and recruitment across centres,  
55 and patients eligible for recruitment to the trial. Interviews will explore participants'  
56 perspectives of the trial, views on the presentation of study information,  
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3 understanding of trial processes (e.g. randomisation), and reasons underlying  
4 decisions to accept or decline the trial. In addition, interviews with staff and other  
5 individuals involved in the trial will explore perspectives on the trial design and  
6 protocol; views about the evidence on which the trial is based; perceptions of  
7 uncertainty/equipoise for themselves and their colleagues; methods for identifying  
8 eligible patients; views on eligibility, and examples of actual recruitment successes  
9 and difficulties. Interview topic guides will be used to ensure similar topic areas are  
10 covered across interviews, while still providing the scope for participants to raise  
11 issues of pertinence to them.

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17 - Audio recording of consultations between healthcare staff and potentially eligible  
18 patients across centres to understand the recruitment process at each centre and to  
19 identify and investigate the challenges to recruitment. The QRI researcher will listen  
20 to and qualitatively analyse the appointments, documenting instances such as  
21 unclear, insufficient or imbalanced information provision and unintentional  
22 transferring of clinician treatment preferences to patients.
- 23  
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26  
27 - Observation of Trial Management Group (TMG) and investigator meetings to gain an  
28 overview of trial conduct and overarching challenges (logistical issues, etc.).  
29

30  
31 An account of the anonymised findings from all the data will be fed back to the Chief  
32 Investigator and TMG. The data will be used by the QRI team to provide supportive and  
33 confidential individual and group feedback to recruiters to help them to communicate  
34 equipoise, balance treatment options and explain to patients the benefits and purposes of  
35 trial participation, whilst optimising informed consent.  
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### 39 40 **Statistical analyses**

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42  
43 The data will be analysed for randomised patients according to intention to treat and follow  
44 Consolidated Standards of Reporting Trials (CONSORT) guidelines. Analyses will be  
45 adjusted for site and for design factors included in the cohort minimisation (e.g. age,  
46 performance status and cell type).  
47  
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51 Survival time and progression free survival time from randomisation will be compared using  
52 survival methods, allowing for censoring of any participant who is either alive or lost to  
53 follow-up at the end of the follow-up period. Patient reported outcome scores (HRQoL EQ-  
54 5D-5L and QLQ-C30) will be compared using a mixed regression model, adjusted for  
55 baseline measures where appropriate. Changes in treatment effect with time will be  
56 assessed by adding a treatment x time interaction to the model and comparing models using  
57 a likelihood ratio test. Deaths will be accounted for by modelling survival and HRQoL jointly.  
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3 Model fit will be assessed using standard methods and alternative models and/or  
4 transformations will be explored if appropriate. Treatment differences and 95% confidence  
5 intervals will be reported.  
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9 Missing data on patient questionnaires will be dealt with according to the scoring manuals.  
10 Multiple imputation methods will be used if greater than 5% of cases have missing data,  
11 otherwise complete case analysis will be undertaken. Compliance rates will be reported,  
12 including the number of participants who have withdrawn from the study, have been lost to  
13 follow-up or died. Causes of death for trial participants will be recorded.  
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17  
18 Frequencies of adverse events will be described. The proportion of participants experiencing  
19 one or more serious adverse events in the two-year follow-up period will be compared using  
20 a generalised linear model.  
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24 Two subgroup analyses are planned: i) comparing primary and secondary outcomes by the  
25 experience level of the surgical site; and ii) comparing the primary outcome by type of  
26 mesothelioma (epithelioid, sarcomatoid or biphasic). An exploratory analysis investigating  
27 the effect of surgeon (surgical group only) will be performed for the primary outcome.  
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31 No interim analyses are planned. The primary analysis will take place when follow-up is  
32 complete for all recruited participants.  
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### 36 **Economic evaluation**

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38 The economic evaluation will compare the costs and effects of surgery versus no surgery,  
39 following established guidelines as set out by NICE.<sup>20</sup> The within-trial cost-effectiveness  
40 analysis will be undertaken from an NHS and personal social services perspective, with a  
41 time horizon from time of consent to 24 months post-randomisation. The primary outcome  
42 measure for the economic evaluation will be quality adjusted life years (QALYs), estimated  
43 using the EuroQol EQ-5D-5L at each follow up timepoint.<sup>15 16</sup> Resource use data collection  
44 will be integrated into the trial CRFs for chemotherapy cycles and surgery (if applicable, this  
45 will include details of the surgical procedure, length of stay in hospital by level of care, and  
46 post-operative complications) and be collected at each follow up timepoint.  
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54 Unit costs will be sought to value resource use data, and the total costs per participant  
55 calculated. Responses to the EQ-5D-5L will be assigned valuations according to NICE  
56 guidance at the time of analysis,<sup>21</sup> and combined with survival to calculate QALYs gained  
57 per participant. Missing resource use and EQ-5D-5L data will be handled using multiple  
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3 imputation methods.<sup>22</sup> From the average costs and QALYs gained in each trial group, the  
4 incremental cost-effectiveness ratio will be derived, producing an incremental cost per QALY  
5 gained of surgery compared to no surgery. Sensitivity analyses will assess the impact of  
6 varying key parameters on baseline cost-effectiveness results. Results will be expressed in  
7 terms of a cost-effectiveness acceptability curve, which indicates the likelihood that surgery  
8 is cost-effective for different levels of willingness to pay for health gain.  
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### 13 **Ethics and dissemination**

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16 The study intervention is already routinely used in the NHS. This study has been reviewed  
17 and given favourable opinion by the London - Camberwell St. Giles Research Ethics  
18 Committee (REC; reference 13/LO/1481) on 7th November 2013. The pilot study was  
19 managed by Papworth Trials Unit Collaboration and the main trial is managed by the Bristol  
20 Trials Centre Clinical Trials and Evaluation Unit and sponsored by Royal Brompton &  
21 Harefield NHS Foundation Trust. Each participant has the right to withdraw at any time. In  
22 addition, the investigator may withdraw the participant from their allocated treatment group if  
23 a clinical reason for not performing the surgical intervention is discovered. If a participant  
24 wishes to withdraw, any data already collected will be included in the study analyses, unless  
25 the participant expresses a wish for their data to be excluded. Withdrawing patients will be  
26 asked if they would continue in follow up and complete the requisite questionnaires.  
27 Participants who choose to withdraw from the study will be treated according to their  
28 hospitals' standard procedures.  
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38 The findings will be disseminated by usual academic channels, i.e. presentation at  
39 international meetings and peer-reviewed publications. A full report for the funder will be  
40 written on completion of the study and a lay summary of the results provided to patients.  
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42  
43

### 44 **Major changes to protocol**

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46 Since the first study protocol was approved by the REC (the current version is v6.0, 10 April  
47 2019), the following changes have been made:  
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- 50
- 51 • Qualitative assessment sub-study added, as part of the pilot phase only.
- 52 • The EuroQol EQ-5D-5L was added.
- 53 • Updates to transition from pilot phase to main study, including addition of the
- 54 integrated QRI and economic evaluation, and removal of the collection of blood and
- 55 tissue samples, and one of the disease specific questionnaires – the EORTC QLQ
- 56 LC-13.
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- 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 1<sup>st</sup> 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

1  
2  
3 UK- United Kingdom  
4

5 **Acknowledgements**

6 The MARS 2 trial is sponsored by The Royal Brompton and Harefield NHS Foundation  
7 Trust. The sponsor will be responsible for the oversight of the MARS 2 study and to ensure  
8 the trial is managed appropriately. We want to thank the large teams at each hospital who  
9 work on the MARS 2 study (representatives from each are listed below). We would also like  
10 to thank Dr Fiona McDonald from the Royal Marsden Hospital, Dr Nagmi Qureshi from  
11 Papworth Hospital and Professor Simon Padley from the Royal Brompton Hospital for their  
12 radiotherapy advisory roles. Thank you also to Professor Andrew Nicholson for his  
13 histopathology advisory role for MARS 2.  
14  
15  
16

17 **Collaborators**

18 **\*MARS 2 Trialists**

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37  
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39 **Papworth Trials Unit Collaboration (pilot study):**

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43 Jane Elliott, Clinical Project Manager  
44 Claire Matthews, Trial Manager  
45 Philip Noyes, Trial Administrator  
46  
47  
48

49 **Participating Sites Members: pilot study and main trial**

50 ***University Hospitals of Leicester NHS Trust – medical and surgical site (opened***  
51 ***22/04/2015)***

52 Dean Fennell, Principal Investigator, Chair of Thoracic Medical Oncology  
53 Apostolos Nakas, Consultant Thoracic Surgeon  
54 Louise Nelson, Research Nurse

55 ***Sheffield Teaching Hospitals NHS Foundation Trust – medical and surgical site (opened***  
56 ***13/05/2015)***

57 John Edwards, Principal Investigator, Consultant Thoracic Surgeon  
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59  
60

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2  
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6 Helena Stanley, Mesothelioma UK Clinical Nurse Specialist

7 **South Tyneside and Sunderland NHS Foundation Trust – medical site (opened**  
8 **19/06/2015)**

9 Liz Fuller, Principal Investigator, Consultant Respiratory Physician

10 Judith Moore, Clinical Trials Officer

11 **Papworth Hospital NHS Foundation Trust – medical site (opened 01/07/2015)**

12 Robert Rintoul, Principal Investigator, Honorary Consultant Respiratory Physician

13 Suzanne Miller, Clinical Trials Coordinator

14 Amy Gladwell, Clinical Trials Administrator

15 Jenny Castedo, Research Nurse

16 Amanda Stone, Senior Research Nurse

17 **Colchester Hospital University NHS Foundation Trust – medical site (opened**  
18 **03/11/2015)**

19 Dakshinamoorthy Muthukumar, Principal Investigator, Consultant Oncologist

20 Charlotte Ingle, Co-Investigator, Consultant Clinical Oncologist

21 Hayley Hewer, Research Nurse

22 **South Tees Hospitals NHS Foundation Trust – medical site (opened 16/11/2015)**

23 Talal Mansy, Principal Investigator, Consultant Medical Oncologist

24 Louise Li, Co-Investigator, Consultant Medical Oncologist

25 Eleanor Aynsley, Co-Investigator, Consultant Clinical Oncologist

26 Andrea Watson, Clinical Trials Coordinator

27 Charlotte Jacobs, Clinical Trials Coordinator

28 **The Clatterbridge Cancer Centre NHS Foundation Trust – medical site (opened**  
29 **25/11/2015)**

30 Tony Pope, Principal Investigator, Consultant in Clinical Oncology

31 Alison Hassall, Research Nurse

32 Masuma Begum, Clinical Trials Assistant

33 **University Hospitals of Derby and Burton NHS Foundation Trust – medical site,**  
34 **(opened 26/11/2015)**

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36 Christopher Worth, Cancer Clinical Research Nurse Lead

37 Ellie Piggott, Research Practitioner

38 Elizabeth Nadin, Research Practitioner

39 **Leeds Teaching Hospitals NHS Trust – medical site (opened 02/12/2015)**

40 Richard Milton, Principal Investigator, Consultant Thoracic Surgeon

41 Victoria Ashford-Turner, Research Nurse

42 Matthew Callister, Respiratory Consultant

43 **Manchester University NHS Foundation Trust – medical site (opened 21/12/2015)**

44 Paul Taylor, Principal Investigator

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8  
9 ***The Royal Wolverhampton NHS Trust – medical site (opened 04/01/2016)***

10 Pek Koh, Principal Investigator, Consultant Clinical Oncologist

11 Ian Morgan, previous Principal Investigator, Consultant Cardiothoracic Surgeon

12 Victoria Lake, Research Nurse

13 Nichola Harris, Research Nurse

14  
15 ***Royal Gwent Hospital, Aneurin Bevan University Health Board – medical site (opened***  
16 ***08/02/2016)***

17 Andreea Alina Ionescu, Principal Investigator, Consultant Respiratory Physician

18 Simon Hodge, Research Nurse

19  
20 ***The Royal Marsden NHS Foundation Trust – medical site (opened 08/04/2016)***

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13 Dr Maria Coakley, Sub-Investigator  
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15 Dr Narda Chaabouni, Sub-Investigator  
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23 ***Peterborough City Hospital, North West Anglia NHS Foundation Trust – medical site***  
24 *(opened 16/05/2016)*

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29

30 **Participating Sites Members: main trial only**

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38 ***The Beatson West of Scotland Cancer Centre, Greater Glasgow Health Board –***  
39 *medical site (opened 14/07/2017)*

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42 ***Golden Jubilee National Hospital – surgical site (opened 14/07/2017)***

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45 Julie Buckley, Research Nurse  
46 Elizabeth Boyd, Research Nurse

47 ***North Bristol NHS Trust – medical site (opened 28/02/2018)***

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**Norfolk and Norwich University Hospitals NHS Foundation Trust – medical site (opened 12/06/2018)**

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**University Hospitals Plymouth NHS Trust – medical site (opened 16/07/2018)**

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**University Hospitals Birmingham NHS Foundation Trust – medical site (opened 03/01/2019)**

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**Independent Trial Steering Committee members**

Prof Marcus Flather MBBS FRCP (Chair), Clinical Professor in Medicine; Dr Paul Beckett, Consultant Respiratory Physician; Miss Carol Tan, Consultant Thoracic Surgeon - has declared the following competing interest: ethicon endostaplers – consultancies; Prof Fergus Gleeson FRCP FRCR, Professor of Radiology and Consultant Radiologist; Prof Fergus MacBeth, Consultant Oncologist; Hon Dr Mavis Nye, Patient Advocate; Dr Harvey Pass, Professor of Thoracic Oncology; Dr Pauline Leonard, Consultant Medical Oncologist – has declared the following competing interests: Teva, Amgen, LCO Pharma; Prof Tom Treasure MS MD FRCS FRCP, Clinical Operations Research Unit.

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

### **Independent Data Monitoring and Safety Committee members**

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

### **Contributors**

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, Principal Investigator and acquired data for the study; SP - Study design, preparation of protocol and review of manuscript, Principal Investigator and acquired data for the study; RR - Study design, preparation of protocol and review of manuscript, Principal Investigator and acquired data for the study; DW - Study design, preparation of protocol and review of manuscript, acquired data for the study; CA - Review of manuscript, Principal Investigator and acquired data for the study; AB - Review of manuscript, Principal Investigator and acquired data for the study; LF - Review of manuscript, Principal Investigator and acquired data for the study; AAI - Review of manuscript, Principal Investigator and acquired data for the study; MK - Review of manuscript, Principal Investigator and acquired data for the study; AK - Review of manuscript, Principal Investigator and acquired data for the study; PK - Review of manuscript, Principal Investigator and acquired data for the study; KL - Review of manuscript, Principal Investigator and acquired data for the study; TM - Review of manuscript, Principal Investigator and acquired data for the study; NAM - Review of manuscript, Principal Investigator and acquired data for the study; RM - Review of manuscript, Principal Investigator and acquired data for the study; DM - Review of manuscript, Principal Investigator and acquired data for the study; TP - Review of manuscript, Principal Investigator and acquired data for the study; AR - Review of manuscript, Principal Investigator and acquired data for the study; RS - Review of manuscript, Principal Investigator and acquired data for the study; JS - Review of manuscript, Principal Investigator and acquired data for the study; ZT - Review of manuscript, Principal Investigator and acquired data for the study; PT - Review of manuscript, Principal Investigator and acquired data for the study; ST - Review of manuscript, Principal Investigator and acquired data for the study; KA - Study design, preparation and drafting of protocol and manuscript, oversight study conduct and acquisition of data; RAH - Statistical analysis plan, review of manuscript; KJ - Preparation and drafting of manuscript, oversight study conduct and acquisition of data; BW - Drafting of manuscript, oversight study conduct and acquisition of data; NM - Conduct of integrated qualitative study, preparation of study protocol, review of manuscript; ES - Design of health economic component, preparation of study protocol, review of manuscript; CAR - Study design, sample size and statistical analysis plan, drafting of protocol, review of manuscript.

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5

6  
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11

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### 20 21 **Disclaimer**

22 The views and opinions expressed therein are those of the authors and do not necessarily  
23 reflect those of the HTA programme, NIHR, NHS or the Department of Health and Social  
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25

26  
27 The funder and sponsor approve any amendments to the study but have no direct  
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29 writing of the report; and the decision to Submit this report for publication.  
30

### 31 32 **Competing interests' statement**

33 EL: reports personal fees from Abbott Molecular, personal fees from Glaxo Smith Kline,  
34 personal fees from Pfizer, personal fees from Novartis, personal fees from Covidien,  
35 personal fees from Roche, personal fees from Lilly Oncology, personal fees from Boehringer  
36 Ingelheim, personal fees from Medela, grants and personal fees from ScreenCell, personal  
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51 grant to ESMO Congress 2018, was sponsored by Boeringer Ingelheim, West Midlands UK  
52 Oncology Specialist Trainee Regional Training Day April 2018, meeting was sponsored by  
53 Roche, Servier and Bristol Myers Squibb in the purchase of exhibition stand space, Eisai  
54 was sponsoring this meeting towards the cost of catering. TM: reports other from MSD, other  
55 from Roche, other from Tesaro, from AstraZeneca, personal fees from Tesaro, personal fees  
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3 from Roche, personal fees from MSD, personal fees from Amgen, other from BMS (outside  
4 the submitted work); KA: reports grants from NIHR HTA, during the conduct of the study;  
5 RAH: reports grants from NIHR HTA, during the conduct of the study; KJ: reports grants  
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9 Institute for Health Research, during the conduct of the study.  
10  
11

12  
13 Unless otherwise stated above, authors have declared no competing interests.  
14

#### 15 **Patient Consent for publication**

16 Not required.  
17

#### 18 **Ethics Approval**

19 This study received a favourable opinion by the London - Camberwell St. Giles Research  
20 Ethics Committee (REC; reference 13/LO/1481) on 7th November 2013.  
21  
22

#### 23 **Provenance and peer review**

24 Not commissioned, externally peer reviewed.  
25  
26

#### 27 **Data sharing**

28 Data will not be made available for sharing until after publication of the main results of the  
29 study. Thereafter, anonymised individual patient data will be made available for secondary  
30 research, conditional on prior consent having been given by the patients and assurance from  
31 the secondary researcher that the proposed use of the data is compliant with the Medical  
32 Research Council (MRC) Policy on Data Sharing regarding scientific quality, ethical  
33 requirements and value for money. A minimum requirement with respect to scientific quality  
34 will be a publicly available pre-specified protocol describing the purpose, methods and  
35 analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The  
36 second file containing patient identifiers would be retained for record linkage or a similar  
37 purpose, Subject to confirmation that the secondary research protocol has been approved by  
38 a UK REC or other similar, approved ethics review body.  
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45 Joyce: 0000-0002-5539-7178; Chris A Rogers: 0000-0002-9624-2615  
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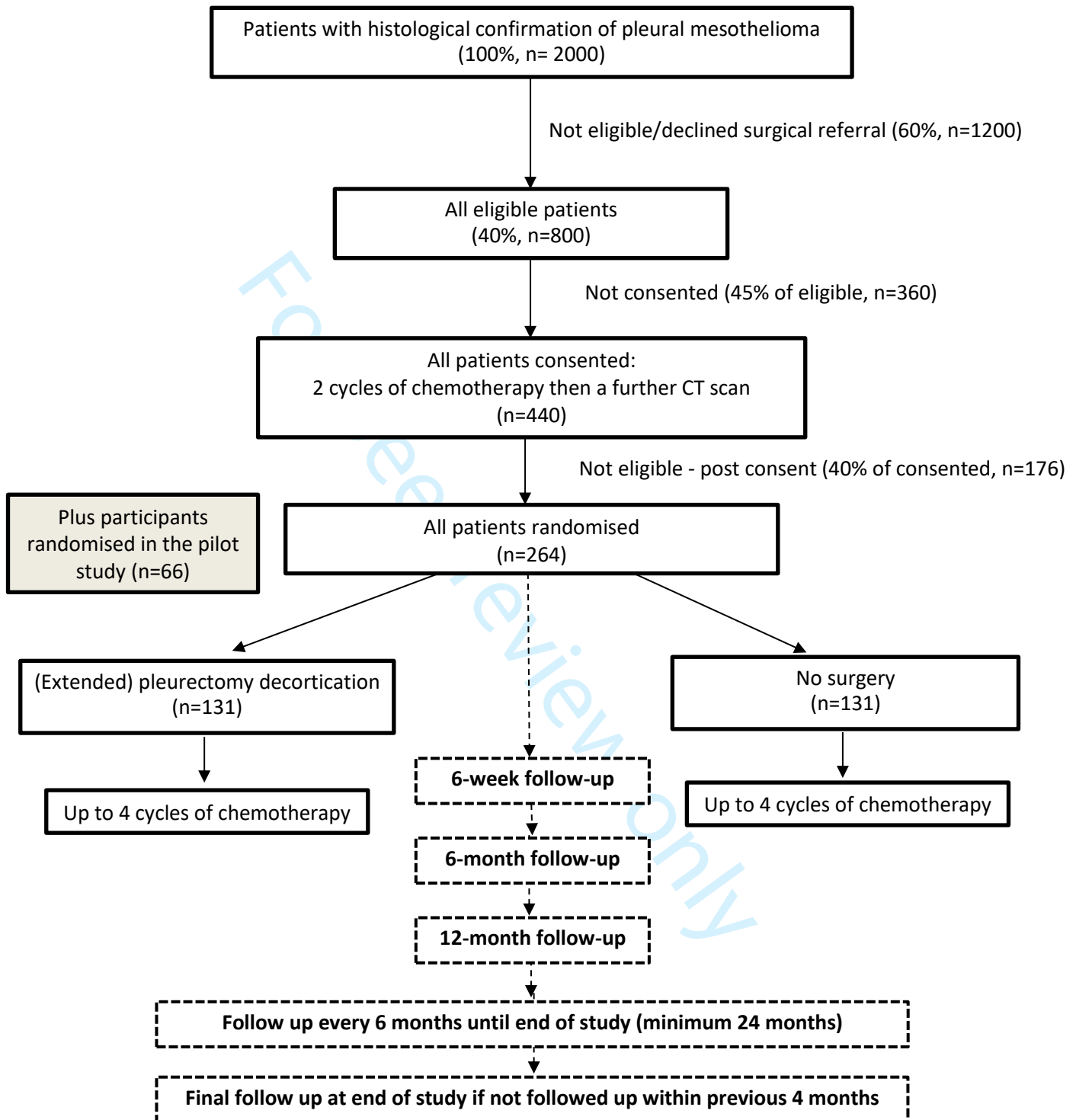
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For peer review only

**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
<b>Administrative information</b>			
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

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant 5,6  
4 rationale studies (published and unpublished) examining benefits and harms for each intervention  
5

6 6b Explanation for choice of comparators 6  
7

8 Objectives 7 Specific objectives or hypotheses 6,7  
9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), 7  
11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)  
12  
13

14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will 7,8  
17 be collected. Reference to where list of study sites can be obtained  
18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and 8  
20 individuals who will perform the interventions (eg, surgeons, psychotherapists)  
21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be 8,9  
23 administered  
24

25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose 8,9  
26 change in response to harms, participant request, or improving/worsening disease)  
27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence 7,8, 13,14  
29 (eg, drug tablet return, laboratory tests)  
30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial 9  
32

33 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood 9-11  
34 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,  
35 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen  
36 efficacy and harm outcomes is strongly recommended  
37

38 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for 11  
39 participants. A schematic diagram is highly recommended (see Figure)  
40  
41  
42

1	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
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12-14
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

10	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
----	---------------------	-----	--	---

16	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
----	----------------------------------	-----	---	---

21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
----	--------------------	-----	---	----

27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
----	--	-----	--	-----

31 **Methods: Data collection, management, and analysis**

33	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
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39		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
----	--	-----	---	-------

1	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
2				
3				
4				
5	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
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
9				
10		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
11				
12				
13				
14	<b>Methods: Monitoring</b>			
15				
16	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
17				
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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
23				
24				
25	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
26				
27				
28	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
29				
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31				
32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15,16
35				
36				
37	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
38				
39				
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
5				
6				
7	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
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23, 24
11				
12				
13	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
14				
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17	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
18				
19				
20	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
21				
22				
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24				
25		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	On request
32				
33				
34	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
35				
36				

\*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. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.