BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-079108
Article Type:	Original research
Date Submitted by the Author:	21-Aug-2023
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Keywords:	Randomized Controlled Trial, QUALITATIVE RESEARCH, Thoracic surgery < SURGERY, Clinical Trial, ONCOLOGY

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Strategies to address recruitment to a randomised trial of surgical and non-surgical treatment for cancer – results from a complex recruitment intervention within the Mesothelioma and Radical Surgery 2 (MARS 2) study

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Abstract

Objectives Recruiting to randomised trials is often challenging particularly when the intervention arms are markedly different. The MARS 2 randomised controlled trial compared standard chemotherapy with or without (extended) pleurectomy decortication surgery for malignant pleural mesothelioma. Anticipating recruitment difficulties, a QuinteT Recruitment Intervention (QRI) was embedded in the main trial phase to unearth and address barriers. The trial achieved recruitment to target within a COVID-19 pandemic adjusted timeframe. This paper presents the key recruitment challenges, and the strategies delivered to optimise recruitment and informed consent.

Design A multi-faceted, flexible, mixed method approach to investigate recruitment obstacles drawing on data from staff/patient interviews, audio-recorded study recruitment consultations and screening logs. Key findings were translated into strategies targeting identified issues. Data collection, analysis, feedback, and strategy implementation continued cyclically throughout the recruitment period.

Setting Secondary thoracic cancer care

Results Respiratory physicians, oncologists, surgeons, and nursing specialists supported the trial, but recruitment challenges were evident. The study had to fit within a framework of a thoracic cancer service considered overstretched where patients encountered multiple healthcare professionals and treatment views, all of which challenged recruitment. Clinician treatment biases, shaped in part by the wider clinical and research context alongside experience, adversely impacted several aspects of the recruitment process by restricting referrals for study consideration, impacting eligibility decisions, affecting the neutrality in which the study and treatment was presented and shaping patient treatment expectations and preferences. Individual and group recruiter feedback and training raised awareness of key equipoise issues, offered support, and shared good practice to safeguard informed consent and optimise recruitment.

Conclusions With bespoke support to overcome identified issues, recruitment to a challenging RCT of surgery versus no surgery in a thoracic cancer setting with a complex recruitment pathway and multiple health professional involvement is possible.

Strengths and limitations of this study

- Embedding a complex recruitment intervention into a randomised trial deemed difficult to recruit to enabled key challenges to be identified and addressed in 'real time'
- Findings were triangulated from multiple qualitative and quantitative data sources
- Over a third of health care professionals approached were not interviewed and we did not have audio-recordings of consultation discussions from half of the sites
- Ability to feedback and engage with individual recruiters on recruitment to study discussions was not always possible, resulting in a written report being sent with no confirmation it was read

Keywords: Randomized Controlled Trial, Recruitment, Qualitative Research, Equipoise, Mesothelioma, Thoracic surgery

Introduction

Challenges of recruiting to randomised controlled trials (RCTs) are well recognised [1-3]. Just over a quarter of respiratory trials and half of surgical trials fail to recruit to their target sample [4-7]. Recruitment failure is reported as the prevalent reason for premature closure of surgical trials [8]. Challenges tend to be more pronounced in trials comparing markedly different interventions, such as surgical versus non-surgical treatment, where issues around equipoise are likely to be heightened [9].

Malignant pleural mesothelioma is a cancer of the lining of the chest wall affecting over 2500 people each year in the UK [10]. Prognosis is poor with long term survival ranging from 4-18 months and a 5-year survival rate less than 10% [11-12]. Whilst there have been advances in systemic treatments, surgery in the form of pleurectomy decortication (removal of the diseased lining of the chest and lung) or extended pleurectomy decortication (involving additional removal of the lining of the heart and/or diaphragm), remains the most commonly performed procedure worldwide in an attempt to improve survival despite no randomised evidence of its effectiveness.

The MARS 2 multi-centre RCT (ISRCTN 44351742) was conducted in the UK to determine whether (extended) pleurectomy decortication alongside chemotherapy is superior to chemotherapy alone with respect to overall survival for patients with pleural mesothelioma [13]. The study anticipated recruitment challenges given the interventions being very different, so a QuinteT Recruitment Intervention (QRI) [14] was embedded in the main phase of the study to support recruitment. The QRI is a flexible, tailored complex intervention that triangulates multiple qualitative strategies and quantitative data to identify and address recruitment difficulties as they arise in real time [14]. Having been embedded in over 70 trials, it has led to insights about recruitment issues and the development of targeted strategies that have improved recruitment [14,15]. The aim of the QRI in MARS 2 was to understand the recruitment process and how it operates in clinical centres, so that sources of difficulties could be identified, and suggestions made to optimise the process. Despite anticipated and identified challenges with recruitment, the MARS 2 study successfully recruited to target within a COVID-19 pandemic adjusted timeframe. This paper illustrates the key challenges and describes the actions undertaken to mitigate barriers to support the conduct of this, and future trials, with divergent treatment arms in a cancer setting.

Methods

The MARS 2 study

The MARS 2 study has been detailed previously [13]. Adults with a diagnosis of malignant pleural mesothelioma were primarily introduced to the study by respiratory physicians and/or oncologists alongside nursing/research specialists, assessed for eligibility by oncologists and surgeons (often in different hospitals) and referred back to the local medical team for study consent. Following two cycles of chemotherapy, consented patients were reassessed for eligibility and randomised to continue with chemotherapy alone or receive surgery and further chemotherapy. The study opened to recruitment in May 2015 with an initial 2-year internal pilot phase and continued through the main study phase until the recruitment target of 328 patients had been reached. The planned recruitment end date was 31 July 2020, but recruitment was paused March-June 2020 due to the COVID-19 pandemic. Once the pause was lifted, sites re-started recruitment in a staggered way, depending on capacity, and recruitment was extended until 31 December 2020. The recruitment target was achieved in November 2020.

Patient and public involvement

Patient and public representatives were involved in the design of the trial, selection of the primary outcome measure and the definition of the minimally important difference in relative survival, and development of patient facing study documents. The Trial Steering Committee also included a PPI representative.

The QRI in the MARS 2 study

The QRI in MARS 2 was only integrated within the main phase of the trial and entailed two core phases as detailed elsewhere [13,14]. QRI Phase 1 aimed to understand the recruitment process at sites and key challenges that had the potential to hinder recruitment. Methods included mapping eligibility and recruitment pathways, interviewing a purposive maximum variation sample of study/site staff and patients, audio-recording study recruitment consultations and reviewing patient-facing documentation. Topic guides, adapted from previous QRI studies and refined to explore emerging findings as the study progressed, were used flexibly in the interviews. Interview and recruitment consultation recordings were transcribed verbatim, and along with recruitment screening logs, were subject to simple counts, content and thematic analyses led by NM [16-18]. Particular attention was paid in the consultation recordings for instances of unclear, insufficient or imbalanced information provision and unintentional transferring of clinician treatment biases to patients. Preliminary analysis, drawing together data from the various sources to identify and understand common challenges, informed further data collection. NM, NF and DE, as experienced qualitative/QRI researchers who conducted the interviews, independently analysed a proportion of transcripts to assess the dependability of coding, and met regularly to review coding and descriptive findings, agree further sampling and discuss theoretical development alongside findings from screening logs.

Findings from Phase 1 were and fed back to the Chief Investigator (CI) and trial management group (TMG) as key issues arose. Effective strategies, tailored to address issues identified in MARS 2, were devised and actioned (QRI Phase 2). Phase 1 and 2 continued cyclically until recruitment target was reached. QRI training, based on the QuinteT RCT recruitment training intervention [19], was additionally delivered prior to QRI Phase 1 to tackle barriers that had emerged in the pilot phase [20] and previous QRI studies [21-25].

Results

QRI sample

As part of the QRI, 19/25 study sites consented to audio-record recruitment discussions. We obtained 55 consultation recordings with 16 study recruiters from 12 sites lasting a mean of 49 minutes. Between December 2017 and March 2020, we undertook 25 interviews with 24 study staff (of 39 invited) from 18 sites lasting 40 minutes on average. The sample consisted of 9 oncologists, 6 research nurses/practitioners/co-ordinators, 5 surgeons, 3 respiratory/chest physicians and 1 TMG member. Additionally, we conducted 21 interviews with 20 patients from five sites who had been invited to participate in MARS 2. Findings from patient interviews have been reported elsewhere [26], although they fed into the interpretation of findings presented herein.

Recruitment challenges

MARS 2 was described by the health professionals as an important study that answers a much-needed question as to the role of pleurectomy decortication for mesothelioma with the potential to change future practice. It was recognised that surgery was currently undertaken in the UK in an *"ad hoc"* and *"unregulated way"* that was unsupported by high-quality evidence. Building the evidence base to address this was the main drive to be part of the study. Challenges with recruitment, however, were evident. These were apparent at all stages of the recruitment process, from patient identification to gaining consent, and were due largely to intellectual and emotional challenges around equipoise compounded by a complex pathway that entailed patient contact with different health professionals and conflicting treatment views.

Organisational challenges of conducting mesothelioma research

Complex pathways

Many site staff described recruitment challenges stemming from the complex study pathway that involved receiving and referring patients for time-sensitive investigations and treatment from different specialists and hospitals. Some patients were referred to MARS 2 sites by local centres which were not involved in the RCT, meaning their standard of care was arranged through other hospitals with additional visits related to MARS 2 being carried out at study sites. Study sites relied on colleagues from neighboring hospitals being aware of MARS 2 and referring patients for consideration. Established regional mesothelioma multi-disciplinary team (MDT) meetings were recognised as crucial for identifying potentially eligible patients, but where sites weren't operating within this structure referrals were sometimes more ad hoc leading to missed patients or delayed referrals making patients ineligible (Table 1, Quote 1). Pressures of a busy service were noted as exacerbating the problem. Trying to fit the MARS 2 study and its complex pathway and timings into a service that was perceived as *"already stretched"* was deemed challenging. Delays in investigations and chemotherapy meant that some patients became ineligible, or they declined the study as they were not willing to accept further treatment delays. Staff capacity issues resulted in one site having to temporarily pause receiving referrals for study consideration. As recruitment progressed, investigator fatigue was offered as an explanation for a slowdown of recruitment and a potential for 'coasting', if sites met what they set as their recruitment target.

Competing research agendas

With the *"explosion of interest in immunotherapies"* and molecular treatment showing promise, a competing research agenda was proposed as hindering recruitment. Studies that should have been complementary and not overlapping in terms of patient selection were considered by some as competing, with clinicians either deciding which study the patient would be best suited for or presenting the options for the patient to decide.

Tension between clinical versus personal equipoise

Hesitancy in referring patients for study consideration

Doubts about the effectiveness of surgery for mesothelioma were evident across specialities. These were driven by findings from previous RCTs showing other types of surgery as not improving survival [27,28] and potentially causing harm [28], and a belief that the condition should not be treated with chemotherapy or surgery due to its poor prognosis. The impact of these views was recognised at all stages of the recruitment process. They were felt to account for fewer than expected study referrals from neighbouring sites and colleagues, or patients coming to discuss the study with a firm idea of

their treatment plan, which often accorded with the previous specialist's view (Table 1, Quotes 2, 3). This was described as making the study discussion challenging.

Bias in determining eligibility

Although study recruiters described uncertainty around the effectiveness of pleurectomy decortication across the clinical community (i.e. clinical equipoise), and therefore a need for the study, individual levels of equipoise varied. These ranged on a continuum from not believing the surgery will be effective, to being neutral as to its effectiveness, having a 'hunch' that it will be effective (especially regarding a subset of 'young and fit' patients), and in a minority of cases, having a seemingly strong belief in the effectiveness of the surgery. Personal levels of equipoise, though, could vary depending on the individual patient. This created a tension at times between appreciating the clinical equipoise versus personal feelings about what would be right for a particular patient. Recruiters shared their discomforts in deeming a patient eligible when it went against their experience and 'gut feeling' about what they felt would be right for that individual. Older patients, those less physically fit, and those with a sarcomatoid cell-type caused the most discomfort and were less likely to be put forward for the study, even though 'on paper' they fulfilled the eligibility criteria (Table 1, Quotes 4, 5).

Recruiter bias in describing treatments

Bias was also evident at times in the description of treatments given in patient consultations. Study recruiters recognised that they may not have always been in equipoise about surgery but were keen to set any biases aside and explain the study impartially. In practice, although they articulated equipoise to patients by explaining the uncertainty as to the effectiveness of lung sparing surgery, the equipoise was sometimes compromised in the ensuing discussion. This was often indirectly, through choice of words that created an imbalanced description of treatments, for example referring to surgery as *"giving an extra benefit"* as opposed to having *"what traditionally is given for this and hoping for the best" or* describing it as *"experimental"* and a *"pretty horrible operation"*. In a very few cases equipoise was overridden in the study discussion, with the recruiter making clear their treatment biases and steering patients in a particular direction that accorded with their beliefs for that individual. Unsurprisingly, patients tended to go along with the clinician's recommendation. A minority of clinicians also offered patients surgery off trial, bringing into question their level of equipoise (Table 1, Quotes 6, 7).

Discomfort approaching patients at time of diagnosis

Finally, there was an indication that some recruiters, more so research nurses/co-ordinators, were uncomfortable approaching patients about the study at the time of receiving a life limiting diagnosis. If they sensed the patient was overwhelmed, then the conversation about MARS 2 (if raised) was sometimes couched in such a way that recognised this and offered patients a clear way out (Table 1, Quote 8).

Addressing identified recruitment challenges

The recruitment issues identified during Phase 1 of the QRI were fed back to the CI and TMG from September 2018 onwards on a regular basis and actions agreed to address them (Phase 2). Table 2 presents an outline and timelines of the main QRI-informed actions that were implemented. A mix of face-to-face, video, telephone and written documentation was used to feedback findings and engage with study team members at individual, site and whole study level to discuss and address issues. Support focused on maximising the pool of eligible patients in terms of finding, assessing and approaching them, and ensuring that study discussions offered full, clear and balanced information.

There was a particular emphasis on issues around equipoise and good practice for conveying it as identified from the present or previous QRI studies, along with dealing with challenges arising from the complex patient pathway, engaging with patient treatment preferences, and explaining randomisation. This was all set within the recognition of their continued above target achievement and encouragement to keep on track.

Impact of QRI on optimising recruitment and informed consent

Figure 1 shows actual recruitment against target, depicting points of QRI-informed actions that were delivered at greater than individual recruiter and single site level. Actions that were developed and delivered in response to findings from QRI Phase 1 began in October 2018 (start of QRI Phase 2). During QRI Phase 2 there were eight QRI-informed actions delivered beyond individual and single site level, as well as monthly recruitment tips in newsletters. There were also a further 22 actions delivered at individual recruiter and site level not depicted on this graph (See Table 2).

The QRI was integrated throughout the main phase of MARS 2 (including set up) with several actions delivered at study wide level, so it was difficult to evaluate the impact it had on recruitment. The timing of QRI-actions in relation to the recruitment rate in Figure 1 suggests that the actions may have contributed to increasing and maintaining recruitment above target prior to the pandemic. From screening log data, the average number of patients recruited per month per site was 0.27 in September 2018 (just prior to QRI Phase 2 and the roll out of feedback and training), which rose to 0.65 in March 2020 (after delivery of most of the QRI feedback and training and just before the study pause). Analysis of recruitment figures six months before and after recruiters received individual feedback on their study recruitment consultations suggest a dose-response effect. Numbers randomised before and after feedback were not dissimilar in the five sites where only one recruiter had received individual feedback at the time of analysis. The greatest difference was observed in the one site where feedback was given at the same time point to all three recruiters (both individually and as a group). At this site no patients were randomised in the 17 months before feedback and six patients were randomised in the five months after, which represented 43% of their total recruitment over 5.5 years.

Several recruiters who received feedback on their individual recruitment discussions acknowledged the value of it, stating that it had raised awareness of certain issues and that they intended to alter their practice accordingly. An evaluation of before-after tailored feedback showed evidence of advice being implemented and improvements in terms of how the study was introduced, balancing of treatment descriptions, explanation of randomisation, and avoidance of potentially problematic terminology (Table 3). We also identified suggestions and strategies that were given within wider recruitment training sessions and recruitment tips/guidance documents being implemented in study recruitment discussions.

For a very small number of sites (n=4) the recruitment challenges were elicited and discussed but were considered insurmountable. They related to a combination of political, logistical or personal factors that were beyond the scope of the QRI. This resulted in two sites closing to recruitment early, and two sites not recruiting any patients.

Discussion

This study offers important insights into the complexities of conducting research and how, with bespoke support to overcome identified issues, recruitment to a challenging RCT of surgery versus

no surgery in a thoracic cancer setting is possible. The MARS 2 study had to fit within the framework of a service that was considered overstretched where patients encountered multiple healthcare specialities and treatment views along their diagnostic and treatment pathway, all of which challenged recruitment. With advances in medical therapies, the study had to compete with other research studies, draining already tight resources and reducing the pool of potential participants. Research staff had to be comfortable approaching patients about a study at a time when their survival was limited and discussing treatment that they may not have felt was appropriate for all. Specific to MARS 2 was the dependence on time-sensitive tests and investigations, and involvement of surgical specialists often at different hospitals, which further added to the complexities of conducting the research. Having identified key context and trial specific issues, QRI-informed actions were devised and implemented to raise awareness, share good practice and offer support in a bid to safeguard informed consent and optimise recruitment until the recruitment target was reached.

One of the key findings was the varying levels of individual equipoise around the surgical intervention and the impact this had on study recruitment. Despite describing treatment uncertainty within the clinical community, it was clear that not all those involved with the care of mesothelioma patients fully subscribed to this view at a personal level, or in relation to particular patients. In the absence of robust and reliable evidence for pleurectomy decortication, individual levels of equipoise were often shaped by past clinical experiences and findings from earlier trials evaluating other types of surgery for mesothelioma which did not infer survival benefits [27,28] and indicated possible patient harm [28]. Some appeared to struggle with referring, assessing and discussing the study with patients when it conflicted with their clinical judgement. Consequently, there would have been patients fulfilling the eligibility criteria who did not have the opportunity to consider participating in the study and others who may not have received full and balanced information necessary for informed decision-making. Role conflict and challenges with setting aside personal views when determining study eligibility and conveying balance during study and treatment discussion have been identified in other RCTs set within the thoracic and broader cancer/surgical contexts and noted to adversely impact recruitment [22,23,29-34]. These issues are heightened in trials comparing very different interventions [9]. In such trials (including MARS 2), clinicians and patients are more likely to struggle with achieving a position of equipoise because of factors such as strong clinical specialty convictions and a priori treatment preferences which in turn may influence how information about the trial is portrayed and patients' decision to participate [9].

Introducing a randomised trial to a population of mostly older patients who have been subjected to a multitude of investigations from different clinical specialities and diagnosed with a poor-prognosis cancer can be challenging. Interviews with patients conducted in the main phase of MARS 2 [26] concurred with findings from the pilot phase showing that participants had difficulties with the volume and complexity of study information, including understanding of equipoise and randomisation [20]. Audio-recordings of recruitment discussions as part of the QRI in the main trial phase offered insight into these findings, demonstrating at times biased descriptions of treatment options and unclear explanations of randomisation which would have contributed to the observed patient difficulties.

Integrating the QRI marks one of the key strengths of the MARS 2 study. It offers an in-depth and rich understanding of the key (and often hidden emotive) challenges triangulated from multiple data sources, and the ability to share this knowledge and devise strategies to support staff to overcome them whilst recruitment is ongoing [21,22]. The timing of QRI-informed actions against an increased and sustained recruitment rate is suggestive of a positive impact but we cannot rule out other factors that may have contributed to this (particularly the opening of new sites) or infer which

interventions may have been more or less effective. Nor can we say if the recruitment target would have been reached without the QRI. The internal pilot phase did not have integrated QRI and achieved target, although once the number of opened sites peaked recruitment started to steadily decline. Conversely, once the number of opened sites peaked in the main study phase, recruitment continued to steadily rise in time with the delivery of the QRI-informed actions. We also identified evidence of improved study information provision with clearer presentations of equipoise following individual or group tailored consultation feedback, which is likely to have enabled better informed decision-making which may or may not translate into increased recruitment. We appreciate that over a third of staff approached were not interviewed and we did not have audio-recordings of consultation discussions from half of the sites. There may therefore have been further recruitment issues unique to these sites that we were unable to elucidate and address. Furthermore, we experienced difficulties in requesting to meet several recruiters to share individual consultation feedback, resulting in a written report often being sent with no confirmation it was read. Future research should focus on distilling the active components of complex recruitment interventions, defining how such interventions should be deemed successful (e.g. increase in rate of recruitment or a measure of informed consent) and determining the best methods to evaluate their effectiveness.

One of the key findings from the QRI in MARS 2 was the impact that the wider clinical and research context had on views of the study and recruitment to it. Surgery for mesothelioma is controversial [35]. Findings from previous trials – showing other types of surgery for mesothelioma as not being beneficial with potential for harm [27,28] – contributed to the views held by some clinicians within and outside of the study on the appropriateness of surgery and therefore appropriateness of the study. Moreover, the study was set within a clinical context for a rare, life limiting condition that had a convoluted pathway involving cross speciality personnel and exposure to varying views on treatment. With promising new treatments on the horizon, the study also had to compete with other research studies within a resource stretched service. Based on these findings, we recommend understanding the wider context of research at an early stage, both in terms of the clinical setting, pathway and prior research, and the potential impact that this could have on the success of a trial. Pre or early trial meetings and training workshops with site staff to detail current evidence and trial rationale, ascertain usual practice and engage with treatment views could help illuminate and mitigate potential difficulties at outset. Continued exploration along with recruiter feedback and training as recruitment is underway has the potential to help address ongoing discomforts. We also recommend engaging health professionals upstream of the study recruitment discussions in such activities, recognising the impact they can have on numbers of patients put forward for study consideration and patient treatment expectations [36,37]. Outside of a specific trial, broad RCT recruitment training raising awareness of common hidden challenges and strategies to overcome can offer additional opportunities to improve recruitment in future RCTs where recruitment is deemed to be challenging [24,38].

Conclusions

A complex multi-method intervention to optimise recruitment revealed important insights into the challenges of conducting a surgical randomised trial within the thoracic cancer setting. Recruitment occurred in what was considered a resource strapped, research competitive and logistically complicated clinical context. The QRI provided important insights into how clinician treatment biases, which were shaped by the wider clinical and research context alongside experience, had a noticeable adverse impact on multiple aspects of the recruitment process prior to and during study participation discussions. We were able to raise awareness of identified issues and support clinicians

through feedback and training to overcome challenges for effective recruitment and informed decision-making. Recruitment to an RCT with very different treatment options set within a complex recruitment pathway with multiple health professional involvement is possible with bespoke training and support to address key equipoise issues.

Acknowledgements

The MARS 2 study is sponsored by The Royal Brompton and Harefield NHS Foundation Trust. We would like to thank the clinical/research teams and patients at each hospital for their support with the QRI component of MARS 2. We would also like to thank Professor Jenny Donovan for comments on an earlier draft of the manuscript.

Author Contributions

NM, NF and DE are members of the University of Bristol QuinteT (Qualitative research integrated within Trials) research group and formed the QRI team within MARS 2. NM and DE led the design and conduct of the QRI. NF led the patient interview aspect of the QRI as part of her doctoral research. NM conducted the QRI, including data acquisition, analysis and interpretation, in discussion with DE and NF, and drafted the manuscript. EL is the chief investigator for MARS 2, KA and BW are the former/present trial managers, RH is the statistician and CR is the methodological lead. All authors contributed to the design of MARS 2, including the QRI component, and drafting of manuscript for intellectual input.

Funding

The MARS 2 study, with integrated QRI in the main study phase, was funded by the National Institute for Health and Care Research (NIHR) Health Techonology Assessment (HTA) programme (project number 15/188/31). The main phase of the MARS 2 study was designed and delivered in collaboration with the former Bristol Trials Centre Clinical Trials and Evaluation Unit (CTEU) (now the Bristol Trials Centre (BTC), a UK Clinical Research Collaboration (UKCRC) registered clinical trials unit which was in receipt of NIHR Clinical Trials Unit (CTU) support funding. DE was supported by the NIHR Bristol Biomedical Research Centre part way through. NF's PhD was funded by the Medical Research Council (MRC) Network of Hubs for Trials Methodology Research (HTMR) (MR/L004933/2/R9).

Disclaimer The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The funder and sponsor had 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.

Ethical approval

Research ethics approval for the MARS2 study which included the integrated QRI was granted by London – Camberwell St. Giles Research Ethics Committee (reference 13/LO/1481) on 7 November 2013. Participants (research staff and patients) gave written informed consent to participate in the QRI aspect of the MARS 2 study.

Competing interests

None declared.

Data Availability Statement

Data, in terms of de-identified consultation and interview transcripts, are available from the corresponding author upon reasonable request. This is on the condition that the request fulfils the necessary approvals in place for "controlled access" data, that participants have agreed to the optional consent to share their anonymised data, and that participant anonymity or privacy is considered not to be compromised.

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Table 1 – Quotes from interviews supporting identified recruitment challenges

Quote	Organisational challenges of conducting mesothelioma research
1	"I actually came across some patients who had been referred too late and that's because they've been, in absolutely good faith from our point of view, mismanaged in small peripheral district hospitals. I know there has been a lot of effort put into getting them onboard… When you get a patient that's been moved back and forward from district general hospital for about six months, at that point he's either progressed too much or simply deteriorated too much not to be able to have any treatment at all. That is a failure, not just of the trial" (Surg06 at interview)
	Equipoise related issues
	Referral hesitancy
2	"One thing I've been slightly disappointed about is the lack of referrals from my neighbouring Trusts, because I had expected more….I think there is some reluctance from the oncologists in some of the neighbouring Trusts about the MARS 2 study….. I think that potentially they don't believe in surgery….I guess probably because of a lack of evidence of any good from it and there is some evidence of harm (Onc04 at interview)
3	"The other patients are coming from local hospitals and have been discussing the mesothelioma with some other chest physicians. Most of the time, they are already coming with the idea of not wanting anything done. That is a really difficult conversation in the clinic, because clearly the patient already has his own idea of, 'The other doctor told me that I'm going to die. I want to just live the rest of my life in the best way possible. I don't really want to discuss too much with you'" (Surg04 at interview)
	Discomforts around eligibility criteria
4	"I do get patients I see who are eligible and I look at them and think, 'No, you're not going to get through this easily.' …Sometimes you do suggest to patients, 'Although on paper you're okay, I don't think you're fit. You meet the criteria for eligibility, but I just don't think you're strong enough'" (Surg01 at interview)
5	"Sending patients [with sarcomatoid cell type] to [surgical site] away from their families for something that I can't guarantee will do them any good when I know their prognosis is rubbish whatever we do to them, doesn't seem very sensible to me" (Onc04 at interview)
	Imbalanced description of treatment options
6	PATIENT: And I was thinking about it and I talked it over with the lads, and I thought, you know, I think I'd just rather go for the chemotherapy ONCOLOGIST 25: Yeah. I don't think that's the wrong thing for you, to be honest…. I would be more than happy to offer you chemotherapy treatment. I think adding surgery into the mix, particularly when it's quite a bit further away, is probably an additional complication. It's maybe not quite the right thing for you. And it sounds like you've come to that conclusion yourself. And I think that's the right thing. ONCOLOGIST 25 to researcher after: "My patter was rather deliberately weighted a bit on the negative side [in describing surgery] as I really didn't think this trial was the right thing for this patient. So rightly or wrongly the pitch does go along those lines as in practice the surgeons tend to take them on"
7	WIFE: [Surgeon] didn't think it was fair to put him in the trial because he would only get a 50% chance of that operation, and he thought he had a 75%, probably 85% or whatever, better chance of survival or prolonging his life with that operation. So it was him [surgeon] that decided not to put him in the trial…. PATIENT: His words were, 'Mr 'Baldwin', I just put a few years on your life
	Discomfort approaching patients
8	"There's a lot going on, they're newly diagnosed patients, we've hit them with a massive amount of information, a massive amount of life-changing information… So if they're feeling a bit like they've got information overload already, then pushing them down that route, you don't want to make them more distressed. Sometimes it's not right for everyone…. I have had one or two patients where we've got a little way into the process and I've got a feel that they're- and I will say to them, 'This is not compulsory. If you feel that it's all a bit much for you and it's a bit overwhelming then maybe the trial's not for you, and that's fine. You just need to let me know that you don't want to take it any further'. That has happened with one patient and he said, 'Do you know what? You're right. I really don't want to think

	about it right now'. And that's fine…. What I do then is just bob them back into the standard of care system" (RN/P/C13 at interview)

Table 2: Key QRI-informed actions with timelines in MARS 2

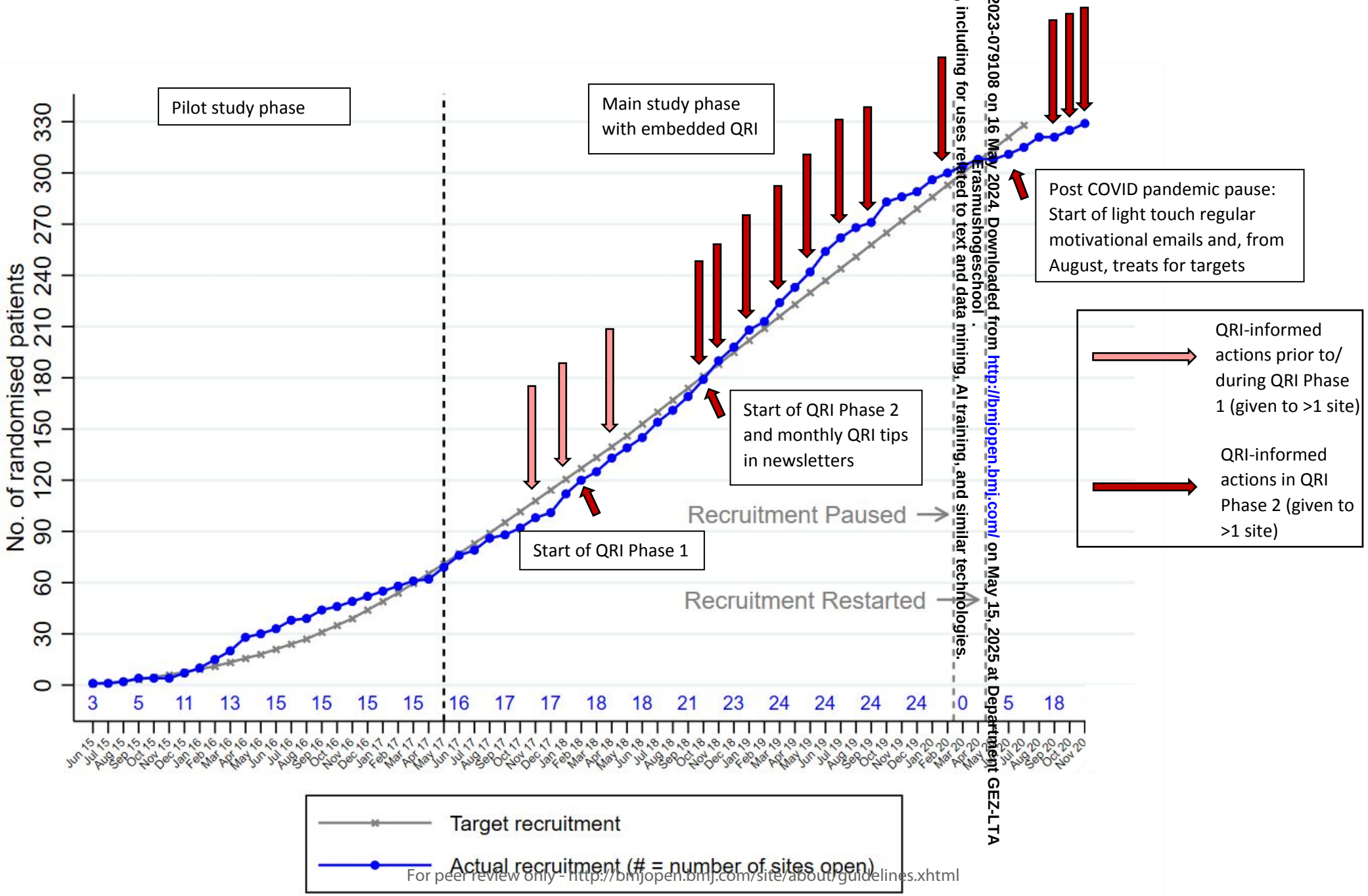
Date	Action	Delivered to (mode)	
Oct 2017	Feedback on patient information leaflet to ensure non-leading descriptions of study treatments	Trial team (written)	QRI-informed actions prior to/during Phase 1
Nov 2017	Recruitment session to raise awareness of common RCT recruitment challenges and tips to deal with them at MARS 2 investigator's meeting	Recruiting site staff (Face-to-face)	
Jan 2018	1-day QRI-informed trial recruiter training day open to any surgeon who recruits to RCTs (not specific to MARS2)	3 recruiters from 2 sites (Face-to-face)	
Feb-Sep 2018	Site initiation or refresher visits with short presentation and discussion to raise awareness of likely recruitment challenges and QRI-informed tips to deal with them	9 sites (7 Video; 2 face-to-face)	
Apr 2018	Tips document for discussing the study with patients based on anticipated issues	Recruiting site staff (Email)	
Sep 2018	Suggested changes to text for CRUK webpage to ensure clear and balanced study description	Patients (Webpage)	
Oct 2018 - Oct 2019	Monthly recruitment tips in study newsletter addressing issues raised from QRI Phase 1	Recruiting site staff (Email)	QRI-informed actions in Phase 2
Oct 2018 – Jun 2020	Individual study recruitment consultation feedback	11 recruiting staff from 13 sites (Email, 1 verbal)	
Oct 2018	Site feedback of equipoise issues from study recruitment consultation recordings	All recruiting staff at 1 site (written, verbal)	
Nov 2018	Phase 1 feedback and discussion on equipoise at surgeons meeting	3 MARS 2 surgeons of 12 invited (Face-to-face)	
Jan 2019	Phase 1 feedback and discussion on key identified issues at BTOG conference meeting	12 attendees (Face-to-face)	
Mar 2019	Recruiting tips document updated to address key findings from Phase 1	Recruiting site staff (Email)	
May 2019	Phase 1 feedback and discussion at investigator's meeting	Recruiting site staff (Video)	
Jun - Oct 2019	Site feedback visit with a focus on equipoise issues	4 sites (Face-to-face)	
Jul 2019	Feedback and discussion of patient interview findings	Nurse/co-ordinator recruiting staff (Video)	
Sep 2019	Sharing best practice in response to common patient questions at recruitment	Recruiting site staff (Email)	
Nov 2019 – Sep 2020	Visually enhanced monthly newsletters with more emphasis on QRI findings and extracts of good recruitment discussions	Recruiting site staff (Email)	
Feb 2020	Personalised motivational emails to sites noting areas of exceptional recruitment practice and offering suggestions on areas to focus on	Recruiting site staff (Email)	
Feb 2020	Targeted emails from the CI to address issues identified from ongoing QRI interviews/discussions with sites	Recruiting site staff (Email)	

Table 3 - Implementation of QRI-informed suggestions in recruitment consultations

Before individualised feedback	After individualised feedback
Introducing the study and rationale	
Now with the trial, which is called MARS-2, part of the trial is that you have the chemotherapy straight away, first half of the chemotherapy, then we randomise you either to surgery or not surgery. If you go for surgery have that and then you have further chemotherapy after. If you get the arm of the trial where there is no surgery you just complete the chemotherapy with [oncologist] which is all given here. Surgery, we would have to ask our surgical colleagues who are based in [city] whether they think looking at your scan surgery is an option. And if they did then we would put you in to the trial and at that point of randomisation make a decision as to whether you go in for surgery or not (Resp02)	*And the third option is a trial that we are taking part in, which looks at the combination of surgery with chemotherapy versus chemotherapy…So the process for the…I meant to say study…for the study is to compare the standard treatment which is chemotherapy and then you get randomised either to chemotherapy with standard treatment, or chemotherapy, surgery and then the rest of the chemotherapy. All the chemotherapy would be here, the surgery would be done at [city]….So, they look to take away the mesothelioma and the lining of the lung on that side. It is done with the hope to cure it, again, it is about trying to take away as much as possible…And the reason why it is a study is because we are not certain yet whether that adds anything or not. That is an unknown question (Resp02)*
Balancing treatment descriptions	
I know that there's not many surgeons in the country that like doing this… it's a big, long operation. It's rare for it to be less than 5 or 6 hours. It can frequently be 7, 8, 9 hours long. It takes a lot out of me as much as the patient. And, you know, it isn't to be sniffed at. There are risks. There are risks of infection in the space around the lung, in the wound, in the lung, pneumonia. There's risks of bleeding, we have to leave drains in to get the lung to expand. It often takes 3 drains for a couple of weeks before the bubbling stops. So it is a big operation. I liken it, for most patients, is - I'm afraid I'm brutally honest. It's like being hit by a bus. It is not a small operation. And it's not something that, you know, is clearly the best thing to do (Surg01)	*We set off with the expectation that we can remove everything that we can see and feel, and hope that that is the case, but the question then is whether this is worth it… what are the risks and benefits of this operation? The risks are that it is a big operation…..It does knock the stuffing out of patients….There are risks of infection, bleeding, pain, bubbling from chest drains. It's a huge operation. Therefore, we have to justify those risks in terms of benefits. The [possible] benefits are quality of life and length of life (Surg01)*
Explaining randomisation	
If you go in the study you sign a consent, and if you move on to the second part, after the two cycles you're given a number and that number is put in to a computer that just randomly decides (Onc03)	*Even when you think a treatment sounds logical and sensible, and a good idea, it's very important to assess it in a clinical trial because that's the only way you can really say whether a new treatment is better than the old, standard treatment, okay. So, to assess that, you have to make a comparison and in this study [explains study process]…..and then you're randomly allocated to one of two groups. …. everyone gets the same amount of chemotherapy, but one group gets this surgery in addition, and at the end of the study you should be able to compare the two groups, and any difference between them should be down to the surgery (Onc03).*
Avoiding potentially problematic terminology	
So, what the trial is looking at is, it's not a trial of whether the chemotherapy's useful or not in this situation. We're looking at whether surgery is an option in the future for patients. So basically, that's the, for want of another word, experimental part of the trial. Okay. So, the chemotherapy that is involved in the trial is actually standard, sort of, standard treatment…. Okay. And that's tried and tested	*So, obviously, Dr [respiratory physician] went through what your options are, and one of them was this study, the MARS2 study. As she mentioned, if you go on to the study you will be allocated to one of two groups, one group will have some chemo and then go on to surgery, the other group would have some chemo then continue with the chemo* (ResStaff01)

chemotherapy. So, there's nothing new about that. That's our current treatment (ResStaff01)	

Figure 1: Recruitment to MARS 2 study against recruitment target depicting points of QRI-informed actions beyond individual and single site level



Standards for Reporting Qualitative Research: A Synthesis of Recommendations[a]

O'Brien, Bridget C.; Harris, Ilene B.; Beckman, Thomas J.; Reed, Darcy A.; Cook, David A. Academic Medicine89(9):1245-1251, September 2014.

Authors' response to the recommendations in relation to the paper:

"Overcoming recruitment challenges in a thoracic cancer surgical randomised controlled trial – results of a complex recruitment intervention within the Mesothelioma and Radical Surgery 2 (MARS 2) study"

NB. The QRI triangulates multiple qualitative strategies and quantitative data to rapidly understand the recruitment process and how it is viewed and operationalised. As a mixed-method study it does not easily fit under a single reporting guideline study type. We have completed the SRQR as best fit.

No.	Topic	Item	Author's response
Title and abstract			
S1	Title	Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	We have made the title informative without being excessive wordy
S2	Abstract	Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	Provided
Introduction			
S3	Problem formulation	Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	Provided
S4	Purpose or research question	Purpose of the study and specific objectives or questions	Provided
Methods			
S5	Qualitative approach and research paradigm	Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale[b]	The methodological underpinnings of the QRI are not rooted in any single philosophy or research paradigm. It is pragmatic, drawing on data sources and collection strategies used in different methodologies.

S6	Researcher characteristics and reflexivity	Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	The researchers' level of qualitative experience is stated in the methods section. Researchers did not know the participants in advance and made them aware of the purpose of the interviews and that they were not clinical or involved with the core analysis of the trial
S7	Context	Setting/site and salient contextual factors; rationale[b]	Provided
S8	Sampling strategy	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale[b]	Provided
S9	Ethical issues pertaining to human subjects	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	Provided
S10	Data collection methods	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale[b]	Provided
S11	Data collection instruments and technologies	Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	Provided
S12	Units of study	Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	Provided
S13	Data processing	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/deidentification of excerpts	Provided

S14	Data analysis	Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale[b]	Provided
S15	Techniques to enhance trustworthiness	Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale[b]	Provided
Results/findings			
S16	Synthesis and interpretation	Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	Provided
S17	Links to empirical data	Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	Provided
Discussion			
S18	Integration with prior work, implications, transferability, and contribution(s) to the field	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/ generalizability; identification of unique contribution(s) to scholarship in a discipline or field	Provided
S19	Limitations	Trustworthiness and limitations of findings	Provided
Other			
S20	Conflicts of interest	Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	Provided
S21	Funding	Sources of funding and other support; role of funders in data collection, interpretation, and reporting	Provided

a The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

b The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

BMJ Open

Strategies to address recruitment to a randomised trial of surgical and non-surgical treatment for cancer – results from a complex recruitment intervention within the Mesothelioma and Radical Surgery 2 (MARS 2) study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-079108.R1
Article Type:	Original research
Date Submitted by the Author:	16-Nov-2023
Complete List of Authors:	Mills, Nicola; University of Bristol Faculty of Health Sciences, Bristol Medical School Farrar, Nicola; University of Bristol Faculty of Health Sciences, Bristol Medical School Warnes, Barbara; University of Bristol Faculty of Health Sciences, Bristol Medical School, Bristol Trials Centre Ashton, Kate; University of Bristol Faculty of Health Sciences, Bristol Medical School, Bristol Trials Centre Harris, Rosie; University of Bristol Faculty of Health Sciences, Bristol Medial School, Bristol Trials Centre Rogers, Chris; University of Bristol Faculty of Health Sciences, Bristol Medical School, Bristol Trials Centre Lim, Eric; The Royal Brompton Hospital, Academic Division of Thoracic Surgery; Imperial College London Faculty of Medicine, National Heart and Lung Institute Elliott, Daisy; University of Bristol Faculty of Health Sciences, Bristol Medical School
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Qualitative research, Research methods, Surgery
Keywords:	Randomized Controlled Trial, QUALITATIVE RESEARCH, Thoracic surgery < SURGERY, Clinical Trial, ONCOLOGY

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Strategies to address recruitment to a randomised trial of surgical and non-surgical treatment for cancer – results from a complex recruitment intervention within the Mesothelioma and Radical Surgery 2 (MARS 2) study

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Abstract

Objectives Recruiting to randomised trials is often challenging particularly when the intervention arms are markedly different. The MARS 2 randomised controlled trial compared standard chemotherapy with or without (extended) pleurectomy decortication surgery for malignant pleural mesothelioma. Anticipating recruitment difficulties, a QuinteT Recruitment Intervention (QRI) was embedded in the main trial phase to unearth and address barriers. The trial achieved recruitment to target with a 4-month COVID-19 pandemic related extension. This paper presents the key recruitment challenges, and the strategies delivered to optimise recruitment and informed consent.

Design A multi-faceted, flexible, mixed method approach to investigate recruitment obstacles drawing on data from staff/patient interviews, audio-recorded study recruitment consultations and screening logs. Key findings were translated into strategies targeting identified issues. Data collection, analysis, feedback, and strategy implementation continued cyclically throughout the recruitment period.

Setting Secondary thoracic cancer care

Results Respiratory physicians, oncologists, surgeons, and nursing specialists supported the trial, but recruitment challenges were evident. The study had to fit within a framework of a thoracic cancer service considered overstretched where patients encountered multiple healthcare professionals and treatment views, all of which challenged recruitment. Clinician treatment biases, shaped in part by the wider clinical and research context alongside experience, adversely impacted several aspects of the recruitment process by restricting referrals for study consideration, impacting eligibility decisions, affecting the neutrality in which the study and treatment was presented and shaping patient treatment expectations and preferences. Individual and group recruiter feedback and training raised awareness of key equipoise issues, offered support, and shared good practice to safeguard informed consent and optimise recruitment.

Conclusions With bespoke support to overcome identified issues, recruitment to a challenging RCT of surgery versus no surgery in a thoracic cancer setting with a complex recruitment pathway and multiple health professional involvement is possible.

Strengths and limitations of this study

- Embedding a complex recruitment intervention into a randomised trial deemed difficult to recruit to enabled key challenges to be identified and addressed in 'real time'
- Findings were triangulated from multiple qualitative and quantitative data sources
- Over a third of health care professionals approached were not interviewed and we did not have audio-recordings of consultation discussions from half of the study sites
- Ability to feedback and engage with individual recruiters on recruitment to study discussions was not always possible, resulting in a written report being sent with no confirmation it was read

Keywords: Randomised Controlled Trial, Recruitment, Qualitative Research, Equipoise, Mesothelioma, Thoracic surgery

Introduction

Challenges of recruiting to randomised controlled trials (RCTs) are well recognised [1-3]. Just over a quarter of respiratory trials and half of surgical trials fail to recruit to their target sample [4-7]. Recruitment failure is reported as the prevalent reason for premature closure of surgical trials [8]. Challenges tend to be more pronounced in trials comparing markedly different interventions, such as surgical versus non-surgical treatment, where issues around equipoise are likely to be heightened [9].

Malignant pleural mesothelioma is a rare cancer of the lining of the chest wall affecting over 2500 people each year in the UK [10]. Prognosis is poor with long term survival ranging from 4-18 months and a 5-year survival rate less than 10% [11-12]. Whilst there have been advances in systemic treatments, surgery in the form of pleurectomy decortication (removal of the diseased lining of the chest and lung) or extended pleurectomy decortication (involving additional removal of the lining of the heart and/or diaphragm), remains the most commonly performed procedure worldwide in an attempt to improve survival despite no randomised evidence of its effectiveness.

The MARS 2 multi-centre RCT (ISRCTN 44351742) was conducted in the UK to determine whether (extended) pleurectomy decortication alongside chemotherapy is superior to chemotherapy alone with respect to overall survival for patients with pleural mesothelioma [13]. The study anticipated recruitment challenges given the interventions being very different, so a QuinteT Recruitment Intervention (QRI) [14] was embedded in the main phase of the study to support recruitment. The QRI is a flexible, tailored complex intervention that triangulates multiple qualitative strategies and quantitative data to identify and address recruitment difficulties as they arise in real time [14,15]. Having been embedded in over 70 trials, it has led to insights about recruitment issues and the development of targeted strategies that have improved recruitment [14,16]. The aim of the QRI in MARS 2 was to understand the recruitment process and how it operates in clinical centres, so that sources of difficulties could be identified, and suggestions made to optimise the process. Despite anticipated and identified challenges with recruitment, the MARS 2 study successfully recruited to target with a 4-month COVID-19 pandemic related extension. This paper illustrates the key challenges and describes the actions undertaken to mitigate barriers to support the conduct of this, and future trials, with divergent treatment arms in a cancer setting.

Methods

The MARS 2 study

Recruitment pathway - The MARS 2 study has been detailed previously [13]. Figure 1 summarises the typical study recruitment pathway in the context of usual clinical practice. Adults with a diagnosis of malignant pleural mesothelioma were mostly introduced to the study by respiratory physicians and/or oncologists alongside local research staff at one of 25 medical sites across the UK. Patients were then referred to a thoracic surgeon at one of five trial accredited UK surgical sites (often in different hospitals to the medical site) to determine eligibility and discuss the study in more detail, before typically being referred back to the local medical team for study consent. Following two cycles of chemotherapy, consented patients were reassessed for eligibility and randomised to continue with chemotherapy alone or receive surgery and further chemotherapy. The study opened to recruitment in May 2015 with an initial 2-year internal pilot phase and continued through the main study phase until the recruitment target of 328 patients had been reached. The planned recruitment end date was 31 July 2020, but recruitment was paused March-June 2020 due to the

COVID-19 pandemic. Once the pause was lifted, sites re-started recruitment in a staggered way, depending on capacity, and recruitment was extended until 31 December 2020. The recruitment target was achieved in November 2020.

Flow of participants to the point of randomisation - 1030 patients were assessed for eligibility, 645 were eligible and 335 were randomised. Of the 310 eligible patients who did not consent, most were not approached for consent (n=183), did not consent (n=74) or did not undergo two cycles of chemotherapy and repeat CT scan (n=36).

Patient and public involvement

Patient and public representatives were involved in the design of the trial, selection of the primary outcome measure and the definition of the minimally important difference in relative survival, and development of patient facing study documents. The Trial Steering Committee also included a PPI representative.

The QRI in the MARS 2 study

The QRI in MARS 2 was only integrated within the main phase of the trial (not pilot) and entailed two core phases as detailed elsewhere [13,14]. QRI Phase 1 aimed to understand the recruitment process at sites and key challenges that had the potential to hinder recruitment. Methods included mapping eligibility and recruitment pathways, interviewing a purposive maximum variation sample of study/site staff and patients, audio-recording study recruitment consultations and reviewing patient-facing documentation. Topic guides, adapted from previous QRI studies and refined to explore emerging findings as the study progressed, were used flexibly in the interviews. Interview and recruitment consultation recordings were transcribed verbatim, and along with recruitment screening logs, were subject to simple counts, content and thematic analyses led by NM [15,17,18]. Particular attention was paid in the consultation recordings for instances of unclear, insufficient or imbalanced information provision and transferring of clinician treatment biases to patients. Preliminary analysis, drawing together data from the various sources to identify and understand common challenges, informed further data collection. NM, NF and DE, as experienced qualitative/QRI researchers who conducted the interviews, independently analysed a proportion of transcripts to assess the dependability of coding, and met regularly to review coding and descriptive findings, agree further sampling and discuss theoretical development alongside findings from screening logs.

QRI Phase 1 commenced in March 2018. Findings were fed back to the Chief Investigator (CI) and trial management group (TMG) as key issues arose. Effective strategies, tailored to address identified issues, were devised and implemented from October 2018 (start of QRI Phase 2). Phase 1 and 2 continued cyclically until recruitment target was reached. QRI training, based on the QuinteT RCT recruitment training intervention [19], was additionally delivered prior to QRI Phase 1 (November 2017 to February 2018) to tackle barriers that had emerged in the pilot phase [20] and previous QRI studies [21-25].

Results

QRI sample

As part of the QRI, 19/25 study sites consented to audio-record recruitment discussions. We obtained 55 consultation recordings with 16 study recruiters from 12 sites lasting a mean of 49 minutes. Between December 2017 and March 2020, we undertook 25 interviews with 24 study staff

(of 39 invited) from 18 sites lasting 40 minutes on average. The sample consisted of 9 oncologists, 6 research nurses/practitioners/co-ordinators, 5 surgeons, 3 respiratory/chest physicians and 1 TMG member. Additionally, we conducted 21 interviews with 20 patients from five sites who had been invited to participate in MARS 2. Findings from patient interviews have been reported elsewhere [26], although they fed into the interpretation of findings presented herein.

Recruitment challenges

MARS 2 was described by the health professionals as an important study that answers a much-needed question as to the role of pleurectomy decortication for mesothelioma with the potential to change future practice. It was recognised that surgery was currently undertaken in the UK in an *"ad hoc"* and *"unregulated way"* that was unsupported by high-quality evidence. Building the evidence base to address this was the main drive to be part of the study. Challenges with recruitment, however, were evident. These were apparent at all stages of the recruitment process from patient identification to receiving consent, and were due largely to intellectual and emotional challenges around equipoise compounded by a complex pathway that entailed patient contact with different health professionals and conflicting treatment views.

Organisational challenges of conducting mesothelioma research

Complex pathways

The MARS 2 recruitment pathway involved additional steps to usual clinical practice (Figure 1). Many site staff described recruitment challenges stemming from the complex study pathway that involved receiving and referring patients for time-sensitive investigations and treatment from different specialists and hospitals. Some patients were referred to MARS 2 sites by local centres which were not involved in the RCT, meaning their standard of care was arranged through other hospitals with additional visits related to MARS 2 being carried out at study sites. Study sites relied on colleagues from neighbouring hospitals being aware of MARS 2 and referring patients for consideration. Established regional mesothelioma multi-disciplinary team (MDT) meetings were recognised as crucial for identifying potentially eligible patients, but where sites weren't operating within this structure referrals were sometimes more ad hoc leading to missed patients or delayed referrals making patients ineligible (Table 1, Quote 1). Pressures of a busy service were noted as exacerbating the problem. Trying to fit the MARS 2 study and its complex pathway and timings into a service that was perceived as *"already stretched"* was deemed challenging. Delays in investigations and chemotherapy meant that some patients became ineligible, or they declined the study as they were not willing to accept further treatment delays. Staff capacity issues resulted in one site having to temporarily pause receiving referrals for study consideration. As recruitment progressed, investigator fatigue was offered as an explanation for a slowdown of recruitment and a potential for 'coasting', if sites met what they set as their recruitment target.

Competing research agendas

With the *"explosion of interest in immunotherapies"* and molecular treatment showing promise, a competing research agenda was proposed as hindering recruitment. Studies that should have been complementary and not overlapping in terms of patient selection were considered by some as competing, with a minority of clinicians stating that they either decided which study the patient would be best suited for or they presented the options for the patient to decide.

Tension between clinical versus personal equipoise

Hesitancy in referring patients for study consideration

Doubts about the effectiveness of surgery for mesothelioma were evident across specialities. These were driven by findings from previous RCTs showing other types of surgery as not improving survival [27,28] and potentially causing harm [28], and a belief that the condition should not be treated with chemotherapy or surgery due to its poor prognosis. The impact of these views was recognised at all stages of the recruitment process. They were felt to account for fewer than expected study referrals from neighbouring sites and colleagues, or patients coming to discuss the study with a firm idea of their treatment plan, which often accorded with the previous specialist's view (Table 1, Quotes 2, 3). This was described as making the study discussion challenging.

Bias in determining eligibility

Although study recruiters described uncertainty around the effectiveness of pleurectomy decortication across the clinical community (i.e. clinical equipoise), and therefore a need for the study, individual levels of equipoise varied. These ranged on a continuum from not believing the surgery will be effective, to being neutral as to its effectiveness, having a 'hunch' that it will be effective (especially regarding a subset of 'young and fit' patients), and in a minority of cases, having a seemingly strong belief in the effectiveness of the surgery. Personal levels of equipoise, though, could vary depending on the individual patient. This created a tension at times between appreciating the clinical equipoise versus personal feelings about what would be right for a particular patient. Recruiters shared their discomforts in deeming a patient eligible when it went against their experience and 'gut feeling' about what they felt would be right for that individual. Older patients, those less physically fit, and those with a sarcomatoid cell-type caused the most discomfort and were less likely to be put forward for the study, even though 'on paper' they fulfilled the eligibility criteria (Table 1, Quotes 4, 5).

Recruiter bias in describing treatments

Bias was also evident at times in the description of treatments given in patient consultations. Study recruiters recognised that they may not have always been in equipoise about surgery but were keen to set any biases aside and explain the study impartially. In practice, although they articulated equipoise to patients by explaining the uncertainty as to the effectiveness of lung sparing surgery, the equipoise was sometimes compromised in the ensuing discussion. This was often indirectly, through choice of words that created an imbalanced description of treatments, for example referring to surgery as *"giving an extra benefit"* as opposed to having *"what traditionally is given for this and hoping for the best" or* describing it as *"experimental"* and a *"pretty horrible operation"*. In a very few cases equipoise was overridden in the study discussion, with the recruiter making clear their treatment biases and steering patients in a particular direction that accorded with their beliefs for that individual. Unsurprisingly, patients tended to go along the direction of the clinician's steer. A minority of clinicians also offered patients surgery off trial, bringing into question their level of equipoise (Table 1, Quotes 6, 7).

Discomfort approaching patients at time of diagnosis

Finally, there was an indication that some recruiters, more so research nurses/co-ordinators, were uncomfortable approaching patients about the study at the time of receiving a life limiting diagnosis. If they sensed the patient was overwhelmed, then the conversation about MARS 2 (if raised) was sometimes couched in such a way that recognised this and offered patients a clear way out (Table 1, Quote 8).

Addressing identified recruitment challenges

The recruitment issues identified during Phase 1 of the QRI were fed back to the CI and TMG from September 2018 onwards on a regular basis and actions agreed to address them (Phase 2). Table 2 presents an outline and timelines of the main QRI-informed actions that were implemented. A mix of face-to-face, video, telephone and written documentation was used to feedback findings and engage with study team members at individual, site and whole study level to discuss and address issues. Support focused on maximising the pool of eligible patients in terms of finding, assessing and approaching them by offering practical solutions, for example sharing site-initiated ideas such as viewing and flagging potentially eligible patients from MDT lists in advance and regular contact with lung nurses to ensure patients were not missed from being assessed for eligibility. Or by raising awareness using evidence from QRI data and opening discussion of how biases and discomforts affected whether patients were considered eligible for the study and approached about it. Awareness was also raised of patients being primed towards or against treatment from colleagues prior to study consideration to indicate the value of recruiters exploring what patients had already been told about treatment options, and to promote sharing of information on MARS 2 with wider colleagues especially those encountered by the patient earlier in the pathway.

Support also focused on ensuring that study discussions offered full, clear, and balanced information. There was a particular emphasis on issues around equipoise and good practice for conveying it. In both individual and group feedback sessions, QRI anonymised data were presented to raise awareness of how imbalances of treatment descriptions, for example disproportionate emphasis on potential risks and benefits or language that subtly favoured or deterred a treatment, could steer patients away from the study and towards or against a particular treatment. Examples from consultation recordings were shared and discussed of more neutral ways of describing treatments and of engaging with patient treatment preferences. The recruitment tips document (Supplement 1) offered suggestions for structuring and discussing recruitment consultations in a way that emphasised the uncertainties around the best treatment, with specific aspects of this spotlighted in monthly newsletters using extracts of QRI data. Feedback and support were set within the recognition of site teams continued above target achievement and encouragement to keep on track.

After the COVID-19 study pause was lifted, actions focused on positive encouragement and motivation to help raise the profile of MARS 2 for the final stages of recruitment, respecting the pandemic related pressures that sites were under and the varying capacity that they subsequently had.

Impact of QRI on optimising recruitment and informed consent

Figure 2 shows actual recruitment against target, depicting points of QRI-informed actions that were delivered at greater than individual recruiter and single site level. Actions that were developed and delivered in response to findings from QRI Phase 1 began in October 2018 (start of QRI Phase 2). During QRI Phase 2 there were eight QRI-informed actions delivered beyond individual and single site level, as well as monthly recruitment tips in newsletters. There were also a further 22 actions delivered at individual recruiter and site level (largely tailored feedback of screening log and/or consultation recordings) not depicted on this graph (See Table 2).

The QRI was integrated throughout the main phase of MARS 2 (including set up) with several actions delivered at study wide level, so it was difficult to evaluate the impact it had on recruitment. The

timing of QRI-actions in relation to the recruitment rate in Figure 2 suggests that the actions may have contributed to increasing and maintaining recruitment above target prior to the pandemic. From screening log data, the average number of patients recruited per month per site was 0.27 in September 2018 (just prior to QRI Phase 2 and the roll out of feedback and training), which rose to 0.65 in March 2020 (after delivery of most of the QRI feedback and training and just before the study pause). Analysis of recruitment figures six months before and after recruiters received individual feedback on their study recruitment consultations suggest a dose-response effect. Numbers randomised before and after feedback were not dissimilar in the five sites where only one recruiter had received individual feedback at the time of analysis. The greatest difference was observed in the one site where feedback was given at the same time point to all three recruiters (both individually and as a group). At this site no patients were randomised in the 17 months before feedback and six patients were randomised in the five months after, which represented 43% of their total recruitment over 5.5 years.

Several recruiters who received feedback on their individual recruitment discussions acknowledged the value of it, stating that it had raised awareness of certain issues and that they intended to alter their practice accordingly. An evaluation of before-after tailored feedback showed evidence of advice being implemented and improvements in terms of how the study was introduced, balancing of treatment descriptions, explanation of randomisation, and avoidance of potentially problematic terminology (Table 3). We also identified suggestions and strategies that were given within wider recruitment training sessions and recruitment tips/guidance documents being implemented in study recruitment discussions.

For a very small number of sites (n=4) the recruitment challenges were elicited and discussed but were considered insurmountable. They related to a combination of political, logistical or personal factors that were beyond the scope of the QRI. This resulted in two sites closing to recruitment early, and two sites not recruiting any patients.

Discussion

This study offers important insights into the complexities of conducting research and how, with bespoke support to overcome identified issues, recruitment to a challenging RCT of surgery versus no surgery in a thoracic cancer setting is possible. The MARS 2 study had to fit within the framework of a service that was considered overstretched where patients encountered multiple healthcare specialities and treatment views along their diagnostic and treatment pathway, all of which challenged recruitment. With advances in medical therapies, the study had to compete with other research studies, draining already tight resources and reducing the pool of potential participants. Research staff had to be comfortable approaching patients about a study at a time when their survival was limited and discussing treatment that they may not have felt was appropriate for all. Specific to MARS 2 was the dependence on time-sensitive tests and investigations, and involvement of surgical specialists often at different hospitals, which further added to the complexities of conducting the research. Having identified key context and trial specific issues, QRI-informed actions were devised and implemented to raise awareness, share good practice and offer support in a bid to safeguard informed consent and optimise recruitment. The trial achieved recruitment to target with a 4-month COVID-19 pandemic related extension.

One of the key findings was the varying levels of individual equipoise around the surgical intervention and the impact this had on study recruitment. Despite describing treatment uncertainty within the clinical community, it was clear that not all those involved with the care of mesothelioma

patients fully subscribed to this view at a personal level, or in relation to particular patients. In the absence of robust and reliable evidence for pleurectomy decortication, individual levels of equipoise were often shaped by past clinical experiences and findings from earlier trials evaluating other types of surgery for mesothelioma which did not infer survival benefits [27,28] and indicated possible patient harm [28]. Some appeared to struggle with referring, assessing and discussing the study with patients when it conflicted with their clinical judgement. Consequently, there were patients fulfilling the eligibility criteria who did not have the opportunity to consider participating in the study and others who did not receive full and balanced information necessary for informed decision-making. Role conflict and challenges with setting aside personal views when determining study eligibility and conveying balance during study and treatment discussion have been identified in other RCTs set within the thoracic and broader cancer/surgical contexts and noted to adversely impact recruitment [22,23,29-34]. These issues are heightened in trials comparing very different interventions [9]. In such trials (including MARS 2), clinicians and patients are more likely to struggle with achieving a position of equipoise because of factors such as strong clinical specialty convictions and a priori treatment preferences which in turn may influence how information about the trial is portrayed and patients' decision to participate [9].

Introducing a randomised trial to a population of mostly older patients who have been subjected to a multitude of investigations from different clinical specialities and diagnosed with a poor-prognosis cancer can be challenging. Interviews with patients conducted in the main phase of MARS 2 [26] concurred with findings from the pilot phase showing that participants had difficulties with the volume and complexity of study information, including understanding of equipoise and randomisation [20]. Audio-recordings of recruitment discussions as part of the QRI in the main trial phase offered insight into these findings, demonstrating at times biased descriptions of treatment options and unclear explanations of randomisation which would have contributed to the observed patient difficulties.

MARS 2 recruitment was further challenged by the condition under investigation being a rare cancer. The rarity of the condition makes finding and recruiting enough patients difficult. Rare disease trials tend to be smaller, longer, and more prone to being terminated, withdrawn or suspended compared with those for non-rare conditions [35]. Missed opportunities for referring and approaching patients, as identified in the present study, become even more impactful when the pool of potentially eligible patients is limited at outset. To add to this challenge, the MARS 2 study was investigating a condition that was very active in terms of research to advance medical treatment opportunities. We know from clinician interviews and screening log data that a very small number of patients being considered for MARS 2 were lost to other studies, but we don't know how many patients were lost before MARS 2 was even considered. This puts a further strain on recruiting to a trial that investigates a rare and life limiting cancer where patients are already difficult to find and where there may be discomfort in approaching them about research at such a time. The value of employing methods to understand and address recruitment challenges in such trials, as with the QRI in the present study, is heightened, as are widespread campaigns to encourage patients to proactively seek involvement in clinical studies they might be eligible for [36].

A core strength of the study was the ability to analyse actual practice (audio-recording of recruitment discussions), as opposed to relying on reported practice, and to triangulate findings from multiple data sources to gain an in-depth and rich understanding of the key (and often hidden emotive [21,22]) difficulties. This was done in a relatively short time to enable strategies to be devised and implemented to support recruiting staff whilst recruitment was underway. The MARS 2 study took five years to randomise 335 patients. This is a threefold increase in the rate of

recruitment compared with the next largest surgical trial for mesothelioma – MARS – which randomised 50 patients in three years [28]. The timing of QRI-informed actions against an increased and sustained recruitment rate is suggestive of a positive impact but we cannot rule out other factors that may have contributed to this (particularly the opening of new sites) or infer which interventions may have been more or less effective. Nor can we say if the recruitment target would have been reached without the QRI. The internal pilot phase did not have integrated QRI and achieved target, although once the number of opened sites peaked recruitment started to steadily decline. Conversely, once the number of opened sites peaked in the main study phase, recruitment continued to steadily rise in time with the delivery of the QRI-informed actions. We also identified evidence of improved study information provision with clearer presentations of equipoise following individual or group tailored consultation feedback, which is likely to have enabled better informed decision-making which may or may not translate into increased recruitment. We appreciate that over a third of staff approached were not interviewed and we did not have audio-recordings of consultation discussions from half of the sites. There may therefore have been further recruitment issues unique to these sites that we were unable to elucidate and address. Furthermore, we experienced difficulties in requesting to meet several recruiters to share individual consultation feedback, resulting in a written report often being sent with no confirmation it was read. Future research should focus on distilling the active components of complex recruitment interventions, defining how such interventions should be deemed successful (e.g. increase in rate of recruitment or a measure of informed consent) and determining the best methods to evaluate their effectiveness.

One of the key findings from the QRI in MARS 2 was the impact that the wider clinical and research context had on views of the study and recruitment to it. Surgery for mesothelioma is controversial [37]. Findings from previous trials – showing other types of surgery for mesothelioma as not being beneficial with potential for harm [27,28] – contributed to the views held by some clinicians within and outside of the study on the appropriateness of surgery and therefore appropriateness of the study. Moreover, the study was set within a clinical context for a rare, life limiting condition that had a convoluted pathway involving cross speciality personnel and exposure to varying views on treatment. With promising new treatments on the horizon, the study also had to compete with other research studies within a resource stretched service. Based on these findings, we recommend understanding the wider context of research at an early stage, both in terms of the clinical setting, pathway and prior research, and the potential impact that this could have on the success of a trial. Pre or early trial meetings and training workshops with site staff to detail current evidence and trial rationale, ascertain usual practice and engage with treatment views could help illuminate and mitigate potential difficulties at outset. Continued exploration along with recruiter feedback and training as recruitment is underway has the potential to help address ongoing discomforts. We also recommend engaging health professionals upstream of the study recruitment discussions in such activities, recognising the impact they can have on numbers of patients put forward for study consideration and patient treatment expectations [38,39]. Outside of a specific trial, broad RCT recruitment training raising awareness of common hidden challenges and strategies to overcome can offer additional opportunities to improve recruitment in future RCTs where recruitment is deemed to be challenging [24,40].

Conclusions

A complex multi-method intervention to optimise recruitment revealed important insights into the challenges of conducting a surgical randomised trial within the thoracic cancer setting. Recruitment occurred in what was considered a resource strapped, research competitive and logistically

complicated clinical context. The QRI provided important insights into how clinician treatment biases, which were shaped by the wider clinical and research context alongside experience, had a noticeable adverse impact on multiple aspects of the recruitment process prior to and during study participation discussions. We were able to raise awareness of identified issues and support clinicians through feedback and training to overcome challenges for effective recruitment and informed decision-making. Recruitment to an RCT with very different treatment options set within a complex recruitment pathway with multiple health professional involvement is possible with bespoke training and support to address key equipoise issues.

Acknowledgements

The MARS 2 study is sponsored by The Royal Brompton and Harefield NHS Foundation Trust. We would like to thank the clinical/research teams and patients at each hospital for their support with the QRI component of MARS 2. We would also like to thank Professor Jenny Donovan for comments on an earlier draft of the manuscript.

Author Contributions

NM, NF and DE are members of the University of Bristol QuinteT (Qualitative research integrated within Trials) research group and formed the QRI team within MARS 2. NM and DE led the design and conduct of the QRI. NF led the patient interview aspect of the QRI as part of her doctoral research. NM conducted the QRI, including data acquisition, analysis and interpretation, in discussion with DE and NF, and drafted the manuscript. EL is the chief investigator for MARS 2, KA and BW are the former/present trial managers, RH is the statistician and CR is the methodological lead. All authors contributed to the design of MARS 2, including the QRI component, and drafting of manuscript for intellectual input.

Funding

The MARS 2 study, with integrated QRI in the main study phase, was funded by the National Institute for Health and Care Research (NIHR) Health Techonology Assessment (HTA) programme (project number 15/188/31). The main phase of the MARS 2 study was designed and delivered in collaboration with the former Bristol Trials Centre Clinical Trials and Evaluation Unit (CTEU) (now the Bristol Trials Centre - BTC), a UK Clinical Research Collaboration (UKCRC) registered clinical trials unit which was in receipt of NIHR Clinical Trials Unit (CTU) support funding. DE was supported by the NIHR Bristol Biomedical Research Centre part way through. NF's PhD was funded by the Medical Research Council (MRC) Network of Hubs for Trials Methodology Research (HTMR) (MR/L004933/2/R9).

Disclaimer The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The funder and sponsor had 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.

Ethical approval

Research ethics approval for the MARS2 study which included the integrated QRI was granted by London – Camberwell St. Giles Research Ethics Committee (reference 13/LO/1481) on 7 November

2013. Participants (research staff and patients) gave written informed consent to participate in the QRI aspect of the MARS 2 study.

Competing interests

None declared.

Data Availability Statement

Data, in terms of de-identified consultation and interview transcripts, are available from the corresponding author upon reasonable request. This is on the condition that the request fulfils the necessary approvals in place for "controlled access" data, that participants have agreed to the optional consent to share their anonymised data, and that participant anonymity or privacy is considered not to be compromised.

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Table 1 – Quotes from interviews supporting identified recruitment challenges

Quote	Organisational challenges of conducting mesothelioma research
1	"I actually came across some patients who had been referred too late and that's because they've been, in absolutely good faith from our point of view, mismanaged in small peripheral district hospitals. I know there has been a lot of effort put into getting them onboard… When you get a patient that's been moved back and forward from district general hospital for about six months, at that point he's either progressed too much or simply deteriorated too much not to be able to have any treatment at all. That is a failure, not just of the trial" (Surg06 at interview)
	Equipoise related issues
	Referral hesitancy
2	"One thing I've been slightly disappointed about is the lack of referrals from my neighbouring Trusts, because I had expected more….I think there is some reluctance from the oncologists in some of the neighbouring Trusts about the MARS 2 study….. I think that potentially they don't believe in surgery….I guess probably because of a lack of evidence of any good from it and there is some evidence of harm" (Onc04 at interview)
3	"The other patients are coming from local hospitals and have been discussing the mesothelioma with some other chest physicians. Most of the time, they are already coming with the idea of not wanting anything done. That is a really difficult conversation in the clinic, because clearly the patient already has his own idea of, 'The other doctor told me that I'm going to die. I want to just live the rest of my life in the best way possible. I don't really want to discuss too much with you'" (Surg04 at interview)
	Discomforts around eligibility criteria
4	"I do get patients I see who are eligible and I look at them and think, 'No, you're not going to get through this easily.' …Sometimes you do suggest to patients, 'Although on paper you're okay, I don't think you're fit. You meet the criteria for eligibility, but I just don't think you're strong enough'" (Surg01 at interview)
5	"Sending patients [with sarcomatoid cell type] to [surgical site] away from their families for something that I can't guarantee will do them any good when I know their prognosis is rubbish whatever we do to them, doesn't seem very sensible to me" (Onc04 at interview)
	Imbalanced description of treatment options
6	PATIENT: And I was thinking about it and I talked it over with the lads, and I thought, you know, I think I'd just rather go for the chemotherapy ONCOLOGIST 25: Yeah. I don't think that's the wrong thing for you, to be honest…. I would be more than happy to offer you chemotherapy treatment. I think adding surgery into the mix, particularly when it's quite a bit further away, is probably an additional complication. It's maybe not quite the right thing for you. And it sounds like you've come to that conclusion yourself. And I think that's the right thing. ONCOLOGIST 25 to researcher after: "My patter was rather deliberately weighted a bit on the negative side [in describing surgery] as I really didn't think this trial was the right thing for this patient. So rightly or wrongly the pitch does go along those lines as in practice the surgeons tend to take them on"
7	WIFE: [Surgeon] didn't think it was fair to put him in the trial because he would only get a 50% chance of that operation, and he thought he had a 75%, probably 85% or whatever, better chance of survival or prolonging his life with that operation. So it was [surgeon] that decided not to put him in the trial…. PATIENT: His words were, 'Mr 'Baldwin', I just put a few years on your life
	Discomfort approaching patients
8	"There's a lot going on, they're newly diagnosed patients, we've hit them with a massive amount of information, a massive amount of life-changing information… So if they're feeling a bit like they've got information overload already, then pushing them down that route, you don't want to make them more distressed. Sometimes it's not right for everyone…. I have had one or two patients where we've got a little way into the process and I've got a feel that they're- and I will say to them, 'This is not compulsory. If you feel that it's all a bit much for you and it's a bit overwhelming then maybe the trial's not for you, and that's fine. You just need to let me know that you don't want to take it any further'. That has happened with one patient and he said, 'Do you know what? You're right. I really don't want to think

	about it right now'. And that's fine…. What I do then is just pop them back into the standard of care system" (RN/P/C13 at interview)

Table 2: Key QRI-informed actions with timelines in MARS 2

Date	Action	Delivered to (mode)	
Oct 2017	Feedback on patient information leaflet to ensure non-leading descriptions of study treatments	Trial team (written)	QRI-informed actions prior to/during Phase 1
Nov 2017	Recruitment session to raise awareness of common RCT recruitment challenges and tips to deal with them at MARS 2 investigator's meeting	Recruiting site staff (Face-to-face)	
Jan 2018	1-day QRI-informed trial recruiter training day open to any surgeon who recruits to RCTs (not specific to MARS2)	3 recruiters from 2 sites (Face-to-face)	
Feb-Sep 2018	Site initiation or refresher visits with short presentation and discussion to raise awareness of likely recruitment challenges and QRI-informed tips to deal with them	9 sites (7 Video; 2 face-to-face)	
Apr 2018	Tips document for discussing the study with patients based on anticipated issues	Recruiting site staff (Email)	
Sep 2018	Suggested changes to text for CRUK webpage to ensure clear and balanced study description	Patients (Webpage)	
Oct 2018 - Oct 2019	Monthly recruitment tips in study newsletter addressing issues raised from QRI Phase 1	Recruiting site staff (Email)	QRI-informed actions in Phase 2
Oct 2018 – Jun 2020	Individual study recruitment consultation feedback	11 recruiting staff from 13 sites (Email, 1 verbal)	
Oct 2018	Site feedback of equipoise issues from study recruitment consultation recordings	All recruiting staff at 1 site (written, verbal)	
Nov 2018	Phase 1 feedback and discussion on equipoise at surgeons meeting	3 MARS 2 surgeons of 12 invited (Face-to-face)	
Jan 2019	Phase 1 feedback and discussion on key identified issues at BTOG conference meeting	12 attendees (Face-to-face)	
Mar 2019	Recruiting tips document updated to address key findings from Phase 1	Recruiting site staff (Email)	
May 2019	Phase 1 feedback and discussion at investigator's meeting	Recruiting site staff (Video)	
Jun - Oct 2019	Site feedback visit with a focus on equipoise issues	4 sites (Face-to-face)	
Jul 2019	Feedback and discussion of patient interview findings	Nurse/co-ordinator recruiting staff (Video)	
Sep 2019	Sharing best practice in response to common patient questions at recruitment	Recruiting site staff (Email)	
Nov 2019 – Sep 2020	Visually enhanced monthly newsletters with more emphasis on QRI findings and extracts of good recruitment discussions	Recruiting site staff (Email)	
Feb 2020	Personalised motivational emails to sites noting areas of exceptional recruitment practice and offering suggestions on areas to focus on	Recruiting site staff (Email)	
Feb 2020	Targeted emails from the CI to address issues identified from ongoing QRI interviews/discussions with sites	Recruiting site staff (Email)	

Table 3 - Implementation of QRI-informed suggestions in recruitment consultations

Before individualised feedback	After individualised feedback
Introducing the study and rationale	
Now with the trial, which is called MARS-2, part of the trial is that you have the chemotherapy straight away, first half of the chemotherapy, then we randomise you either to surgery or not surgery. If you go for surgery have that and then you have further chemotherapy after. If you get the arm of the trial where there is no surgery you just complete the chemotherapy with [oncologist] which is all given here. Surgery, we would have to ask our surgical colleagues who are based in [city] whether they think looking at your scan surgery is an option. And if they did then we would put you in to the trial and at that point of randomisation make a decision as to whether you go in for surgery or not (Resp02)	*And the third option is a trial that we are taking part in, which looks at the combination of surgery with chemotherapy versus chemotherapy…So the process for the…I meant to say study…for the study is to compare the standard treatment which is chemotherapy and then you get randomised either to chemotherapy with standard treatment, or chemotherapy, surgery and then the rest of the chemotherapy. All the chemotherapy would be here, the surgery would be done at [city]….So, they look to take away the mesothelioma and the lining of the lung on that side. It is done with the hope to cure it, again, it is about trying to take away as much as possible…And the reason why it is a study is because we are not certain yet whether that adds anything or not. That is an unknown question (Resp02)*
Balancing treatment descriptions	
I know that there's not many surgeons in the country that like doing this… it's a big, long operation. It's rare for it to be less than 5 or 6 hours. It can frequently be 7, 8, 9 hours long. It takes a lot out of [the surgeon]e as much as the patient. And, you know, it isn't to be sniffed at. There are risks. There are risks of infection in the space around the lung, in the wound, in the lung, pneumonia. There's risks of bleeding, we have to leave drains in to get the lung to expand. It often takes 3 drains for a couple of weeks before the bubbling stops. So it is a big operation. I liken it, for most patients, is - I'm afraid I'm brutally honest. It's like being hit by a bus. It is not a small operation. And it's not something that, you know, is clearly the best thing to do (Surg01)	*We set off with the expectation that we can remove everything that we can see and feel, and hope that that is the case, but the question then is whether this is worth it… what are the risks and benefits of this operation? The risks are that it is a big operation…..It does knock the stuffing out of patients….There are risks of infection, bleeding, pain, bubbling from chest drains. It's a huge operation. Therefore, we have to justify those risks in terms of benefits. The [possible] benefits are quality of life and length of life (Surg01)*
Explaining randomisation	
If you go in the study you sign a consent, and if you move on to the second part, after the two cycles you're given a number and that number is put in to a computer that just randomly decides (Onc03)	*Even when you think a treatment sounds logical and sensible, and a good idea, it's very important to assess it in a clinical trial because that's the only way you can really say whether a new treatment is better than the old, standard treatment, okay. So, to assess that, you have to make a comparison and in this study [explains study process]…..and then you're randomly allocated to one of two groups. …. everyone gets the same amount of chemotherapy, but one group gets this surgery in addition, and at the end of the study you should be able to compare the two groups, and any difference between them should be down to the surgery (Onc03).*
Avoiding potentially problematic terminology	
So, what the trial is looking at is, it's not a trial of whether the chemotherapy's useful or not in this situation. We're looking at whether surgery is an option in the future for patients. So basically, that's the, for want of another word, experimental part of the trial. Okay. So, the chemotherapy that is involved in the trial is actually standard, sort of, standard treatment…. Okay. And that's tried and tested	*So, obviously, Dr [respiratory physician] went through what your options are, and one of them was this study, the MARS 2 study. As she mentioned, if you go on to the study you will be allocated to one of two groups, one group will have some chemo and then go on to surgery, the other group would have some chemo then continue with the chemo* (ResStaff01)

chemotherapy. So, there's nothing new about that. That's our current treatment (ResStaff01)	

Figure Legends:

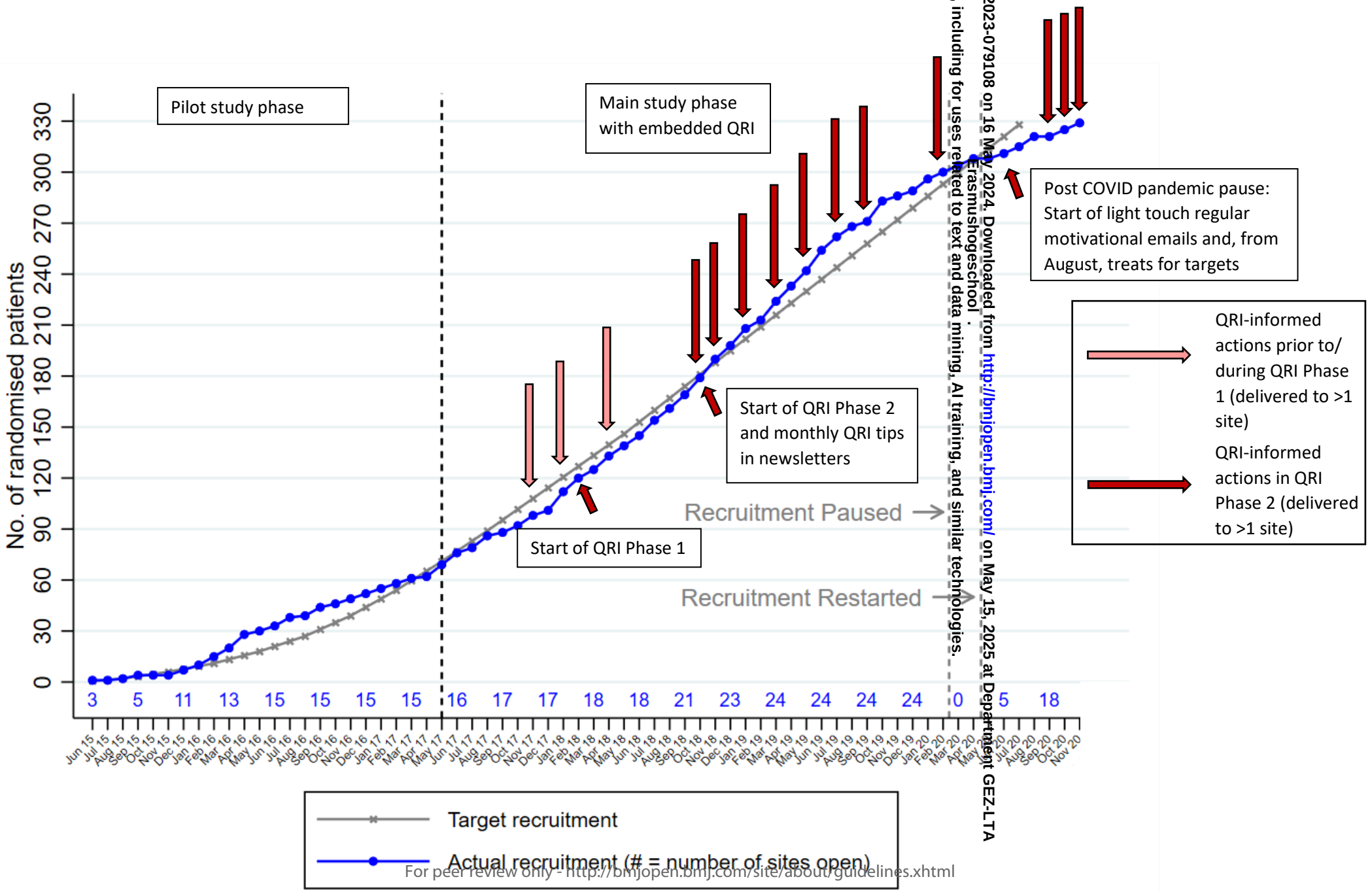
Figure 1: MARS 2 recrutment pathway (with typical clinical pathway in red)

Figure 2: Recruitment to MARS 2 study against recruitment target depicting points of QRI-informed actions beyond individual and single site level

Figure 1: MARS 2 recruitment pathway (with typical clinical pathway in red)

Patients may have seen a number of health care professionals prior to this point for diagnostic tests	Initial checks are done to identify patients and make basic eligibility checks for MARS 2 (e.g.at MDT)		
	↓		
	Patient is given diagnosis by respiratory doctor and asked for permission for their scan (ideally undertaken within the past 4 weeks) to be sent to surgical centre for review	→	Study may be briefly introduced at this point, either in person (by respiratory doctor or local research staff) or over the phone, as a reason for request to send scan. A minority of patients get referred from their local hospital to a study medical centre to hear more about the study. Patient information leaflet given Patients are likely to also meet with oncologist to discuss chemotherapy
	↓		
Surgical centre is likely to be different from where patient is diagnosed	Scan is reviewed at surgical centre	→	If tumour is deemed resectable, patient is invited to speak with surgeon about the study In a minority of centres this may be before initial appointment with oncologist
	↓		
Discussion with doctor (typically oncologist) ± local research staff	Patient is invited back to their medical centre to discuss MARS-2 participation		MARS 2 consent/decline may happen at this visit
	↓		
Chemotherapy is done at medical centre	Patient consents to MARS 2 and starts chemotherapy		This may be at a study medical centre or at the patient's local medical centre
	↓		
	Patient undertakes 2 cycles of chemotherapy and a further CT scan is performed (ideally towards the end of the 2nd week of the 2nd cycle of chemotherapy to avoid treatment delays)	→	CT is reviewed by surgical centre to ensure tumour is still resectable and advises patient's medical team
	↓		
Patients must still have resectable tumour to be randomised	Patient is randomised to receive either chemotherapy alone or chemotherapy plus surgery	→	Depending on randomisation outcome, patient continues with up to 4 cycles of chemotherapy, or is referred back to the surgical centre for surgery then the medical centre to continue with up to 4 cycles of chemotherapy to commence within 12 weeks of surgery

Figure 2: Recruitment to MARS 2 study against recruitment target depicting points of QRI-informed actions by and individual and single site level



Supplement 1: QRI-Informed Recruitment Tips document

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Recruitment and Informed Consent Guidance

March 2019

This document includes suggestions that can help with recruitment and informed consent. You may wish to consider using them alongside your own individual style.

Introducing MARS 2

- Approach all potentially eligible patients so that everyone has an opportunity to consider participation (including those with biphasic and sarcomatoid disease).
- Mention the study early on and explain the equipoise *('Because we don't know if chemotherapy on its own or chemotherapy with surgery is best we're taking part in a study called MARS 2')*. Be mindful to convey equipoise throughout.
- Request patients to *'keep an open mind'* until all information is heard.

Discussing the study

- Present MARS 2 in an enthusiastic and straight-forward manner.
- It is better to use the term 'study' rather than 'trial' as trial means different things to different patients and can therefore be confusing *(e.g. 'trial and error', 'experimental', 'guinea pig').*
- It can be good to mention that MARS 2 is a study funded by the NIHR – the NHS funding body - and is being carried out in over 25 centres around the UK.
- Describe the benefits of study participation, e.g. close follow-up and monitoring, and that the aim of research is to produce evidence so that future patients will not have to face current treatment uncertainties.
- Be clear that participation is voluntary and that their care will not be affected in anyway if they choose not to participate.

Balancing the treatments

- You are not expected to give detailed information about chemotherapy or surgery if you do not specialise in it, but you can still ensure that you convey equipoise throughout the consultation when explaining treatments:
  - Remind patients that we do not know if chemotherapy on its own or in combination with surgery is best, hence the need for the study.
  - When outlining the treatments think 'balance' – are you inadvertently steering patients?
    - Avoid loaded terminology (i.e. 'gold standard', 'experimental')
    - Balance the potential advantages and disadvantages of the treatments e.g.

      "Those are the risks of surgery, but then as I said it comes back to that balance of risks and benefits – what are the potential benefits of surgery with chemotherapy…. How then does this compare with the chemotherapy alone…"
- Patients often ask clinicians what they think is best. Refrain from providing your own personal beliefs to avoid confusing or influencing patients and emphasise equipoise e.g.

  "I think that is a really difficult question because we don't genuinely know which is the best option. We just don't have enough information to say which treatment will be best for which patient, which is why we're doing this study. Both treatments have their pros and cons and have been assessed as being suitable for you. I would be happy to recommend the study to my close friends and family."

Exploring patient preferences

- It can be common for patients to arrive at a consultation with an expectation/preference about what treatment they would like. It is still important to discuss the study fully so that patients can make an informed decision about treatment options and study participation.
- **Strategies for responding to preferences:**
  - Acknowledge their preference and open up the conversation – *"Ok, but…"* is a good way to ensure this, e.g.
    "Ok it's great that you've read up on the surgery, but let's just consider what surgery means"
  - Remind patients to keep an 'open mind' until they've heard all information, e.g.
    "But what I'd like you to do is just keep an open mind whilst I run through the treatments. There may be aspects of treatment that you have not yet considered."
  - Explore the rationale behind their views and their understanding of the treatments. This can reveal misunderstandings or incorrect information, e.g.
    "I know that surgery is your preferred/least preferred option, what is it about surgery that draws you to it/concerns you?"
  - Balance their views, tailored to any concerns they may have, e.g.
    "Ok I accept what you say that surgery with chemotherapy is appealing because the cancer is removed, but we don't know if it makes any difference to your survival and the operation has associated risks. Chemotherapy alone is the current standard of care provided in both arms and does not have the associated risks of surgery."
  - Emphasise the position of uncertainty and not knowing which treatment option is best, e.g.
    "What you've got to remember is that both are good options that are suitable for you. If we knew which one was better we would recommend it."
  - Reassure patients about both treatments, e.g.
    "Neither of the treatments in the study are experimental, they have been used for years. The surgeon and oncologist have deemed them suitable for you."
- Continue with the conversation until you feel they are sufficiently open minded to consider either treatment option, in which case they are in an ideal position to be recruited. If they still have a clear preference, and you are satisfied that they are well-informed following the discussion, then they should not be recruited. This will minimise the risk of crossover.
- Patients preferences often dissipate following gentle exploration and balanced information.

Describing randomisation

- Randomisation is a familiar concept but it can be difficult to explain in a way that makes sense to patients in the context of a trial.
- Randomisation may not make sense to patients if they do not grasp *why* it is being done, so it is important to explain both the purpose and process of randomisation, e.g.
  "We don't know if it's better to have chemotherapy alone or with surgery so we want a fair comparison of the treatment options (purpose). We use a process of randomisation to produce two groups of patients that are similar except for the treatment received (process). This will enable us to do a fair comparison. You will have an equal chance of receiving chemotherapy alone or chemotherapy with surgery. If you or I chose then the groups are unlikely to be the same and the results may not be reliable."
- It is helpful to avoid using terms such as *'toss of a coin'* or *'decided by a computer'*. Metaphors have been viewed as being quite flippant for something so serious, and reference to a computer deciding has led to confusion that the computer is choosing the 'best' option for them.
- Randomisation can actually be a solution to uncertainty if the patient is unsure what to do.

Please ask any questions - thank you for your continued support!

Standards for Reporting Qualitative Research: A Synthesis of Recommendations[a]

O'Brien, Bridget C.; Harris, Ilene B.; Beckman, Thomas J.; Reed, Darcy A.; Cook, David A. Academic Medicine89(9):1245-1251, September 2014.

Authors' response to the recommendations in relation to the paper:

"Overcoming recruitment challenges in a thoracic cancer surgical randomised controlled trial – results of a complex recruitment intervention within the Mesothelioma and Radical Surgery 2 (MARS 2) study"

NB. The QRI triangulates multiple qualitative strategies and quantitative data to rapidly understand the recruitment process and how it is viewed and operationalised. As a mixed-method study it does not easily fit under a single reporting guideline study type. We have completed the SRQR as best fit.

No.	Topic	Item	Author's response
Title and abstract			
S1	Title	Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	We have made the title informative without being excessive wordy
S2	Abstract	Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	Provided
Introduction			
S3	Problem formulation	Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	Provided
S4	Purpose or research question	Purpose of the study and specific objectives or questions	Provided
Methods			
S5	Qualitative approach and research paradigm	Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale[b]	The methodological underpinnings of the QRI are not rooted in any single philosophy or research paradigm. It is pragmatic, drawing on data sources and collection strategies used in different methodologies.

S6	Researcher characteristics and reflexivity	Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	The researchers' level of qualitative experience is stated in the methods section. Researchers did not know the participants in advance and made them aware of the purpose of the interviews and that they were not clinical or involved with the core analysis of the trial
S7	Context	Setting/site and salient contextual factors; rationale[b]	Provided
S8	Sampling strategy	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale[b]	Provided
S9	Ethical issues pertaining to human subjects	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	Provided
S10	Data collection methods	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale[b]	Provided
S11	Data collection instruments and technologies	Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	Provided
S12	Units of study	Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	Provided
S13	Data processing	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/deidentification of excerpts	Provided

S14	Data analysis	Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale[b]	Provided
S15	Techniques to enhance trustworthiness	Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale[b]	Provided
Results/findings			
S16	Synthesis and interpretation	Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	Provided
S17	Links to empirical data	Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	Provided
Discussion			
S18	Integration with prior work, implications, transferability, and contribution(s) to the field	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/ generalizability; identification of unique contribution(s) to scholarship in a discipline or field	Provided
S19	Limitations	Trustworthiness and limitations of findings	Provided
Other			
S20	Conflicts of interest	Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	Provided
S21	Funding	Sources of funding and other support; role of funders in data collection, interpretation, and reporting	Provided

a The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

b The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.