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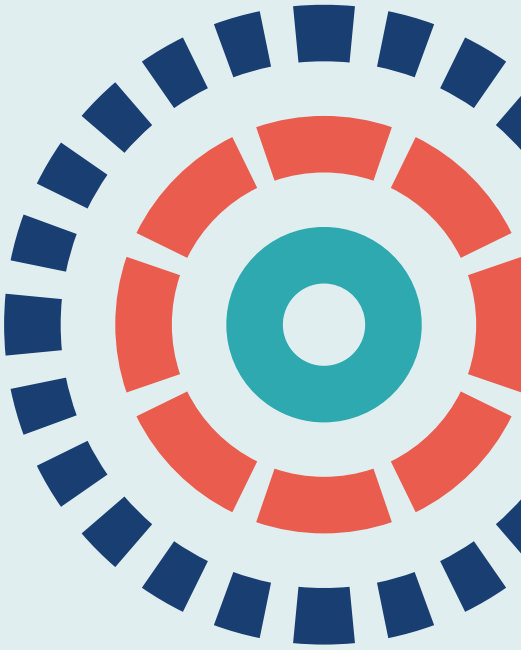

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Liver resection surgery compared with thermal ablation in high surgical risk patients with colorectal liver metastases: the LAVA international RCT

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Abstract

Liver resection surgery compared with thermal ablation in high surgical risk patients with colorectal liver metastases: the LAVA international RCT

Brian Davidson,[1*] Kurinchi Gurusamy,[1] Neil Corrigan,[2] Julie Croft,[2] Sharon Ruddock,[2] Alison Pullan,[2] Julia Brown,[2] Maureen Twiddy,[3,4] Jaqueline Birtwistle,[3] Stephen Morris,[5] Nick Woodward,[6] Steve Bandula,[7] Daniel Hochhauser,[8] Raj Prasad,[9] Steven Olde Damink,[10] Marielle Coolson,[10] K van Laarhoven[11] and Johannes HW de Wilt[11]

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Background: Although surgical resection has been considered the only curative option for colorectal liver metastases, thermal ablation has recently been suggested as an alternative curative treatment. There have been no adequately powered trials comparing surgery with thermal ablation.

Objectives: Main objective – to compare the clinical effectiveness and cost-effectiveness of thermal ablation versus liver resection surgery in high surgical risk patients who would be eligible for liver resection. Pilot study objectives – to assess the feasibility of recruitment (through qualitative study), to assess the quality of ablations and liver resection surgery to determine acceptable standards for the main trial and to centrally review the reporting of computed tomography scan findings relating to ablation and outcomes and recurrence rate in both arms.

Design: A prospective, international (UK and the Netherlands), multicentre, open, pragmatic, parallel-group, randomised controlled non-inferiority trial with a 1-year internal pilot study.

Setting: Tertiary liver, pancreatic and gallbladder (hepatopancreatobiliary) centres in the UK and the Netherlands.

Participants: Adults with a specialist multidisciplinary team diagnosis of colorectal liver metastases who are at high surgical risk because of their age, comorbidities or tumour burden and who would be suitable for liver resection or thermal ablation.

Interventions: Thermal ablation conducted as per local policy (but centres were encouraged to recruit within Cardiovascular and Interventional Radiological Society of Europe guidelines) versus surgical liver resection performed as per centre protocol.

Main outcome measures: Pilot study – patients' and clinicians' acceptability of the trial to assist in optimisation of recruitment. Primary outcome – disease-free survival at 2 years post randomisation. Secondary outcomes – overall survival, timing and site of recurrence, additional therapy after treatment failure, quality of life, complications, length of hospital stay, costs, trial acceptability, and disease-free survival measured from end of intervention. It was planned that 5-year survival data would be documented through record linkage. Randomisation was performed by minimisation incorporating a random element, and this was a non-blinded study.

Results: In the pilot study over 1 year, a total of 366 patients with colorectal liver metastases were screened and 59 were considered eligible. Only nine participants were randomised. The trial was stopped early and none of the planned statistical analyses was performed. The key issues inhibiting recruitment included fewer than anticipated patients eligible for both treatments, misconceptions about the eligibility criteria for the trial, surgeons' preference for one of the treatments ('lack of clinical equipoise' among some of the surgeons in the centre) with unconscious bias towards surgery, patients' preference for one of the treatments, and lack of dedicated research nurses for the trial.

Conclusions: Recruitment feasibility was not demonstrated during the pilot stage of the trial; therefore, the trial closed early. In future, comparisons involving two very different treatments may benefit from an initial feasibility study or a longer period of internal pilot study to resolve these difficulties. Sufficient time should be allowed to set up arrangements through National Institute for Health Research (NIHR) Research Networks.

Trial registration: Current Controlled Trials ISRCTN52040363.

Funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 21. See the NIHR Journals Library website for further project information.

Contents

List of tables

List of figures

List of abbreviations

ALPPS	Associated Liver Partition and Portal vein Ligation for Staged hepatectomy
CIRSE	Cardiovascular and Interventional Radiological Society of Europe
CLM	colorectal liver metastases
CT	computed tomography
DFS	disease-free survival
HPB	hepatopancreatobiliary
HSDR	Health Services and Delivery Research
HTA	Health Technology Assessment
LAVA	Liver Resection Surgery Versus Thermal Ablation for Colorectal LiVer MetAstases
MWA	microwave ablation
NIHR	National Institute for Health Research
PGfAR	Programme Grants for Applied Research
PHR	Public Health Research
PI	principal investigator
PPI	patient and public involvement
Q-QAT	Quanti-Qualitative Appointment Timing
RCT	randomised controlled trial
REC	Research Ethics Committee
RFA	radiofrequency ablation
sMDT	specialist multidisciplinary team

Plain English summary

In about 50% of people with bowel cancer, cancer spreads to the liver (colorectal liver metastases) within 5 years of detection and treatment. Liver resection (i.e. surgical removal of a portion of the liver) is the standard treatment in people below 70 years of age who are otherwise well, provided that the liver cancer is confined to a limited part of the liver. Such patients are considered 'low-risk' patients. Older patients and those with major medical problems or extensive cancers are considered 'high-risk' patients, as they are at a higher risk of developing complications following liver resection. Thermal ablation destroys the liver cancers using a needle that heats the cancer deposits until they are destroyed. There is significant uncertainty as to whether or not ablation can offer equivalent survival compared with surgery for 'high-risk' patients.

We planned and conducted a randomised controlled trial comparing ablation with surgery to resolve this uncertainty. In this trial, some patients received ablation and others received surgery. The treatment was allocated at random with neither patients nor the study organisers choosing the treatment. The trial had an internal pilot (i.e. a smaller version of the full trial to resolve any 'teething problems' and ensure that a sufficient number of participants can be included in the full trial). Only nine patients were recruited in the 1-year internal pilot, compared with the anticipated recruitment of 45 patients. Therefore, the trial closed early as a result of poor recruitment, and the uncertainty about the best treatment for high-risk patients with colorectal liver metastases continues. The main reasons for the poor recruitment included fewer than anticipated eligible participants, clinicians' unconscious bias towards surgery, and patients' preference for one treatment or the other. In the future, comparisons involving two very different treatments may benefit from a feasibility study or a longer period of pilot study to resolve any difficulties.

Scientific summary

Background

Main trial background

Bowel cancer (colorectal cancer) is the second biggest cause of cancer-related death in the UK and the fourth most common cancer. Just under 16,000 colorectal cancer patients die each year in the UK. The main cause of death is the development of colorectal liver metastases. About 20% of patients have liver metastases at presentation and another 30% develop liver metastases subsequently. Surgical resection of colorectal liver metastases is considered the only potentially curative treatment. Therefore, specialist liver resection centres are carrying out more extensive and complex liver resections, including in elderly patients and those with major comorbidities. This more extensive surgery in elderly patients and those with comorbidities (i.e. high-risk patients) is associated with increased morbidity and mortality.

Thermal ablation has lower complication rates and is associated with better health-related quality of life than surgery, but is used mainly when potentially curative surgery is not possible. There has been no adequately powered randomised controlled trial comparing ablation with surgery in patients with colorectal liver metastases. Some retrospective studies have shown that there is a higher rate of local recurrence following thermal ablation than following surgery. Because of this and the lack of long-term data on cancer outcomes, the majority of clinicians feel that it would be unethical to randomise low-risk patients to ablation or surgery, despite the short-term benefits of lower complication rates, less pain and lower costs associated with patients undergoing ablation. Although some non-randomised studies did not justify these concerns and demonstrated equivalent survival between radiofrequency ablation and liver resection despite patients undergoing radiofrequency ablation having more comorbidities or more extensive cancer, another non-randomised study supported these concerns and demonstrated that radiofrequency ablation was associated with poorer 5-year survival than surgery. The only difference between the patient groups in the second study was that treatment followed patient preference for radiofrequency ablation or surgery.

However, with high-risk patients, there is significant uncertainty as to the benefits of surgery, and the majority of clinicians feel that there is equipoise between these modalities for this patient group. Survival rates in this patient group are 1.5–2 times lower than in low surgical risk patients. In this randomised controlled trial, we planned to compare the clinical effectiveness and cost-effectiveness of ablation with that of surgery in this high-risk group of patients. If this research showed equivalent results of thermal ablation and surgery in this group, then thermal ablation could be considered standard of care as it is associated with reduced pain, morbidity, mortality and hospital stay. The data would also provide justification for a subsequent clinical trial on low-risk patients.

Pilot study background

Recruitment to randomised controlled trials with very different treatment arms can be difficult and recruitment to surgical trials is particularly challenging. Qualitative research can identify aspects of the trial design that hinder recruitment and possible solutions, so qualitative work was embedded into the LAVA (Liver Resection Surgery Versus Thermal Ablation for Colorectal LiVer MetAstases) pilot study. Previous studies have shown that patient-related (e.g. difficulties of informed consent, understanding randomisation and preference for certain treatments) and clinician-related (e.g. concern about impact on the doctor–patient relationship, clinical equipoise and how the trial is presented to patient) factors affect recruitment. To anticipate these issues, a training manual was developed based on published guidance and supplemented by research findings. This provided advice about presenting the trial, the evidence base for the LAVA trial, and a step-by-step guide to help recruiters present the information in an unbiased way. The manual was presented at the study launch meeting, a copy was given to each local principal

investigator at site initiation, and this was followed up with telephone-based support. The qualitative substudy aimed to understand barriers to recruitment from the perspective of patients and staff.

Objectives

Pilot study and main trial objectives

The aim of the research is to compare the clinical effectiveness and cost-effectiveness of thermal ablation with that of liver resection surgery in high surgical risk patients who are eligible for liver resection. The main trial primary outcome was disease-free survival at 2 years post randomisation.

The internal pilot study objective was to assess the feasibility of recruitment. The assessments around the interventions were to assess the quality of the ablations and the quality of liver resection surgery in terms of completeness of resection. In addition, the computed tomography scan findings relating to ablation outcomes were centrally reviewed to ensure quality of reporting.

Qualitative study objectives

The aims of the qualitative study during the internal pilot were to explore patients' and clinicians' acceptability of the trial and recruitment processes to inform recruitment and follow-up strategies for the main trial.

Methods

Study design

This was an international (UK and the Netherlands), multisite, open, pragmatic, parallel-group, randomised controlled trial design with an internal pilot. Participants were randomised via Clinical Trials Research Unit telephone or web-based 24-hour randomisation systems on a one-to-one basis to receive either surgical resection or thermal ablation. The trial aim was to recruit 330 participants over a 48-month period. During the internal pilot, 15 centres were required to open for recruitment and 45 participants had to be recruited for the main trial to be considered feasible. It was agreed with the funders at the grant application stage that, if this recruitment target was not met by the end of the pilot, trial continuation would be discussed with the Trial Steering Committee and Data Monitoring and Ethics Committee.

Settings and participants

Participants were recruited from tertiary hepatopancreatobiliary centres in the UK and in the Netherlands. Patients were eligible if they were aged $\geq$ 18 years with a specialist multidisciplinary team diagnosis of colorectal liver metastases that were considered to be resectable or ablatable with curative intent, or were considered to be high risk for surgery by meeting at least one of the following criteria: at high risk because of their age, at high risk because they have major comorbidities as judged by the treating clinician, liver metastases leading to poor prognosis or at high risk because of tumour burden or anticipated small volume of residual liver. Exclusion criteria included incurable extrahepatic metastases that were not suitable for liver resection surgery or thermal ablation, concurrent malignant disease (except basal cell skin carcinoma), planned simultaneous resection of primary and liver metastases, and pregnancy.

Intervention and control

Patients were randomised using minimisation incorporating a random element to surgical resection or thermal ablation to be carried out as per standard practice. The minimum ablation and surgical standards were defined in the Site Standard Operation Procedures and ablation criteria were based on Cardiovascular and Interventional Radiological Society of Europe guidance provided to the centres.

Outcomes

Primary outcome
Disease-free survival at 2 years post randomisation.

Secondary outcomes
Overall survival, timing and site of recurrence, additional therapy after treatment failure, quality of life, complications, length of hospital stay, costs, trial acceptability, and disease-free survival measured from the end of the intervention. It was also planned that 5-year survival data would be documented through record linkage.

Follow-up of participants
Participants would have been reviewed in clinics at 3, 6, 12, 18 and 24 months post randomisation, where they would have received follow-up investigations (computed tomography scans of the chest, abdomen and pelvis) as a minimum and blood tests to check the levels of tumour markers.

Statistical methods

Analysis methods: statistical
Owing to the small sample size and early closure of the trial, it was not possible to perform any of the original planned analysis for the main trial. The intention for the main trial was to assess the difference in disease-free survival at 2 years. The non-inferiority hypothesis would have been tested using an appropriate survival model to incorporate random effects with respect to research sites, and including adjustment for the stratification factors. Differences in rates, such as complication rates and recurrence rates, would have been analysed using multilevel logistic regression incorporating random effects with respect to research site, and would have included adjustment for the stratification factors.

Analysis methods: qualitative study
In-depth, semistructured telephone or face-to-face interviews were conducted with recruiters (i.e. consultants, interventional radiologists and nursing staff), and face-to-face interviews were conducted with patients. Interviews were audio-recorded, transcribed verbatim, anonymised and analysed thematically. This allowed the interpretation of key issues faced by recruiters, and reasons for non-consent from the perspective of patients and staff to be examined. Participant information sessions (recruiter consultation encounters) were audio-recorded (with permission) and were examined using the Q-QAT (Quanti-Qualitative Appointment Timing) approach to allow the analysis of how information was presented by recruiters and received and understood by patients. All patients eligible for the trial and all staff involved in trial recruitment were eligible for interview, with a planned sample size of ≈20 patients (i.e. consenters, decliners and those withdrawing post randomisation) and 15 staff. An iterative approach to sampling was planned, with earlier interviews to be used to inform later recruitment until data saturation was reached.

Sample size
A total of 330 participants were required to demonstrate non-inferiority of thermal ablation with respect to resection in terms of the primary end point (2-year disease-free survival) with 80% power at the 2.5% one-sided level of significance, assuming a median time to event of 14 months in the resection group and a non-inferiority margin for thermal ablation of 4 months, allowing for a 5% drop-out rate.

Results

Patient recruitment
The trial opened in 17 sites (UK, $n = 13$; and the Netherlands, $n = 4$) during the internal pilot phase. Of the 366 patients with colorectal liver metastases screened, 59 were eligible for the trial. Only nine

participants were randomised during the 12-month internal pilot phase, compared with the anticipated recruitment of 45 participants. The trial was stopped early; therefore, the participants were followed up within the trial for 3 months post randomisation. These patients were subsequently followed as per the usual follow-up regimen in the hospital.

Assessing barriers to recruitment and actions taken to increase recruitment

In September 2017, 6 months following commencement of the 1-year pilot phase, sites had identified fewer eligible patients than expected. Closer examination identified that some sites were misapplying the inclusion and exclusion criteria, and the chief investigator visited each site and met with clinical colleagues to remedy these misunderstandings. However, this did not lead to improvements in recruitment. Interviews with staff revealed that, when potentially eligible patients were identified, the specialist multidisciplinary team generally rejected their inclusion in the trial. Few patients (decliners or consenters) consented to be interviewed, so little can be gleaned from their perspective, but there was some evidence from staff interviews that recruiting surgeons struggled to maintain equipoise when presenting the trial.

Prior to study launch, the qualitative study team developed a training manual to help with study introduction, and this was discussed at each site initiation meeting. Follow-up teleconferences were arranged following each site set-up to identify early challenges and to go through the training manual with recruiting staff. However, it was many months between training and the identification of potentially eligible patients; therefore, much of the initial learning was lost. During interviews with staff, we explored training needs, but most sites refused training as they considered that they had a strong track record of recruiting to trials and felt that training was not needed, or had not identified any eligible patients and felt that it was premature to judge if additional training were needed.

Qualitative study results

Thirteen of the 15 planned staff interviews were conducted and these were analysed as intended.

Invitations were sent to 41 staff (i.e. consultants, radiologists and research nurses) at 12 sites, and all of those who consented were interviewed. Interviews took place between November 2017 and February 2018. We conducted in-depth, semistructured interviews that were informed by a topic guide developed in conjunction with patient and public involvement representatives and the existing literature on the barriers (clear obstacles and hidden challenges) to recruitment. All interviews were audio-recorded with permission. The 13 interviews generated 268 minutes of rich audio data.

The original aim was to conduct interviews with up to 20 patients: consenters, decliners and those dropping out post randomisation. Despite regular reminders to sites, significant recruitment problems were encountered. All eligible patients were to be invited to take part in an interview, but only three sites forwarded details of any patients who were willing to be approached for interview. Evidence from conversations with staff and staff interviews suggests that gatekeeping by nurses was an issue, with some nurses being reluctant to approach patients who had already consented for the trial, citing concerns about patient burden (i.e. not wanting to lose a patient who was showing interest in taking part in the trial). Four patients initially consented to interview (all of whom declined trial involvement), but two subsequently declined an interview because of health problems.

Ten sites consented to record recruitment sessions but, despite regular reminders and reassurances that the recordings would remain confidential, only two sites provided any recordings for analysis [six recordings were from one site (one clinician) and one recording was from a second clinician at another site]. A commonly cited barrier to recording the sessions was that the study voice recorder was held by the research nurse, who was not always available when clinicians met with patients.

Conclusions

The feasibility of recruitment in the patient population was not demonstrated during the pilot stage of the trial and, therefore, the trial closed early to recruitment on completion of the pilot stage. The main reasons for the poor recruitment into the trial included fewer than anticipated participants who were eligible for both surgery and ablation, clinician unconscious bias towards surgery, patient preference for one treatment or the other, and lack of dedicated research nurses who could identify and recruit participants to the trial. There were insufficient numbers recruited to allow useful comparison between the two interventions.

Lessons learned

There were several lessons learned during this trial. Studies comparing two very different treatment modalities will benefit from a feasibility study to provide a better estimate of the number of participants eligible for the trial and resolve any misconceptions about participant eligibility. In the absence of a feasibility study, a longer and more intensive phase of internal pilot study would be required to resolve the issues, which might be in the form of more extensive training to avoid unconscious bias of the recruiters and training the referring clinicians so that the patient does not have a preconceived idea of treatment. It is probably prohibitively expensive to have dedicated trial nursing staff for a trial of this nature with an anticipated recruitment of four or five participants per centre per year; therefore, sufficient time should be allowed to identify appropriately trained staff through National Institute for Health Research (NIHR) Research Networks.

With hindsight, it would have been better to conduct the qualitative research interviews prior to recruitment starting to prospectively identify and resolve any difficulties, as well as during the initial months of recruitment. Once set up, the buy-in by the majority of clinicians participating in the specialist multidisciplinary team is critical to the screening and identification of trial candidates and this can be truly judged only once clinicians start to screen patients.

The uncertainty about the relative benefits and harms of thermal ablation compared with liver resection in high surgical risk patients with colorectal liver metastases will remain for the next decade. Surgeons and other members of the specialist multidisciplinary team should be aware of the ongoing lack of evidence to guide the choice of liver resection or thermal ablation in patients with colorectal liver metastases, especially in those who are in a high surgical risk group.

Trial registration

This trial is registered as ISRCTN52040363.

Funding

This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 21. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Liver resection is effective for improving the life expectancy of people with colorectal liver metastases (CLM). However, only about 7–20% of people with CLM undergo liver resections because of the age or comorbidities of the patient or because of the extent of cancer spread. Increasing the number of patients who can undergo potentially curative therapy for liver-only metastases is a main NHS goal for improving the survival of bowel cancer patients in the UK. In the light of this, specialist liver resection centres are carrying out more extensive and complex resections, including in elderly patients with major comorbidities.

Thermal ablation is a lower-risk alternative modality for treatment of CLM and involves the destruction of cancer by heat. Thermal ablation includes established modalities such as radiofrequency ablation (RFA) or microwave ablation (MWA). Thermal ablation may be associated with a lower chance of cure. A systematic review of ablative methods in patients with CLM concluded that there is a group of patients in whom the risk and benefits of surgical resection are less evident and that good-quality evidence is required for the clinical outcome and cost-effectiveness of thermal ablation in comparison with surgery in these high-risk patients.[2]

Thermal ablation could be used for some patients with CLM that are not suitable for surgical resection[3] and is not current practice for patients suitable for liver resection surgery because of higher local recurrence rates with thermal ablation.[4] Multiple studies have highlighted the superiority of surgery to ablation for preventing recurrence within the liver.[4,5] A recent series from Nishiwada *et al.*[4] showed a 13% recurrence after surgery as opposed to 46% after thermal ablation. Other newer modalities of thermal ablation include laser ablation and high-intensity focused ultrasound.[6,7]

To determine the evidence for thermal ablation, a National Institute for Health Research (NIHR) Health Technology Assessment (HTA)-funded systematic review of literature was commissioned and subsequently published in February 2014.[8] We reviewed this information along with subsequently published literature. To our knowledge, there are no adequately powered trials comparing surgery with thermal ablation therapy in patients with CLM.

The systematic review identified one non-randomised study in which the survival in patients who had received RFA was similar to that of liver resection surgery despite the RFA group having more comorbidities and more extensive liver metastases.[9] An exploratory cost-effectiveness analysis performed by the group on the basis of this non-randomised study showed that RFA has the potential to be cheaper and might result in better health-related quality of life. Another non-randomised study published since this systematic review reported that patients undergoing RFA had survival rates comparable to those undergoing surgery, despite having more extensive liver metastases.[5] Similarly, an underpowered randomised controlled trial (RCT) showed no difference in survival between MWA and liver surgery in resectable CLM.[10] However, in another non-randomised study published after the systematic review by Loveman *et al.*,[8] people who were eligible for surgery but preferred RFA had poorer survival than those undergoing surgery.[11]

Background: pilot study of 1 year

Recruitment to RCTs with very different treatment arms can be difficult, and recruitment to surgical trials is particularly challenging.[12] Qualitative research can identify aspects of the trial design that hinder recruitment and detect possible solutions,[13,14] so qualitative work was embedded into the LAVA (Liver Resection Surgery Versus Thermal Ablation for Colorectal LiVer MetAstases) pilot study.[1] Studies show that patient-related (e.g. difficulties of informed consent, understanding randomisation and preference for certain treatments) and clinician-related (e.g. concern about impact on the doctor–patient relationship, clinical equipoise and how the trial is presented to patient) factors affect recruitment.[13–16] To anticipate these issues, a training manual, based on published guidance and supplemented by research findings, was developed.[13,17,18] This provided advice about presenting the trial, the evidence base for the LAVA trial and a step-by-step guide to help recruiters present the information in an unbiased way. The manual was presented at the study launch meeting, a copy was given to each local principal investigator (PI) at site initiation, and this was followed up with telephone-based support. The qualitative substudy aimed to understand barriers to recruitment from the perspective of patients and staff.

Chapter 2 Methods

Objectives

The purpose of the main trial was to compare the clinical effectiveness and cost-effectiveness of thermal ablation with liver resection surgery in high surgical risk patients who were eligible for liver resection.

An internal pilot study was run in the first year of recruitment and the objectives were to assess the feasibility of recruitment, the quality of ablations and the quality of liver resection surgery to determine acceptable standards for the main trial and to centrally review the reporting of computed tomography (CT) scan findings and recurrence (in both arms) to ensure quality of reporting.

The aims of the qualitative study were to:

- explore patient and clinician acceptability of the trial and recruitment processes/study procedures to assist in optimisation of recruitment
- explore clinical equipoise in the liver surgery community
- understand how information is presented to recruiters, in particular explore the content and style of delivery and feed this back promptly to recruiters to improve practice.

Patient and public involvement aims

Two patient and public involvement (PPI) representatives were identified to inform key aspects of the pilot study, in particular:

- to ensure that the design and wording of all information sheets and consent forms were presented in a clear and accessible manner
- to provide input into the topic guide for the participant interviews (pilot study)
- interpretation of the qualitative results
- to ensure that the content and the format of the dissemination of trial findings were relevant and appropriate to patients
- to ensure that the patient representatives were supported to provide input into the pilot study.

Trial design

The LAVA trial was a prospective, international (UK and the Netherlands), multisite, open, pragmatic, parallel-group, RCT design with an internal pilot to investigate the clinical effectiveness and cost-effectiveness of thermal ablation (RFA or MWA) compared with liver resection for the treatment of patients with resectable CLM who would be considered as high risk for surgery and with a low chance of cure.

The target was 330 participants (165 in each arm) to be recruited into the trial over a planned 48-month recruitment period.

Participants

Participants who met the eligibility criteria below were recruited from tertiary hepatopancreatobiliary (HPB) centres in the UK and in the Netherlands (see *Appendix 1*).

Inclusion criteria

1. Aged ≥ 18 years.
2. Able to provide written informed consent.
3. With a specialist multidisciplinary team (sMDT) diagnosis of CLM that were considered to be resectable or ablatable with curative intent.
4. Resected colorectal primary or plan for primary resection with curative intent.
5. Met at least one of the following criteria:

    i. Those considered high risk for surgery because of their age (e.g. aged > 70 years).
    ii. Those with major comorbidities, as judged by the treating clinician (e.g. previous transient ischaemic attack, major cerebrovascular accidents, myocardial infarction, severe chronic airway disease, previous pulmonary embolism, chronic kidney disease).
    iii. Those with liver metastases with poor prognosis [e.g. requiring down-staging with chemotherapy prior to definitive treatment, poor response after chemotherapy but still resectable and ablatable, curable extrahepatic disease (randomised following treatment of extrahepatic disease), multiple synchronous metastases, previous treated lung metastases (resection or ablation)].
    iv. High-risk surgery [e.g. need for two-staged liver resection or Associated Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS) or portal vein or small anticipated remnant liver volume].
    v. Those with recurrence of CLM following previous surgery or ablation.

6. Suitable candidate for both liver resection surgery and thermal ablation as judged by the sMDT (suitability assessment included general fitness).
7. Able and willing to comply with the terms of the protocol including quality-of-life questionnaires.

Exclusion criteria

1. Incurable extrahepatic metastases.
2. Concurrent malignant disease (except basal cell carcinoma).
3. Planned simultaneous resection of primary and liver metastases.
4. Pregnancy (it was the local site's responsibility to ensure that this was assessed in women of child-bearing potential in accordance with local standard of care).

Summary of protocol amendments

The summary of protocol amendments is shown in *Table 1*.

TABLE 1 Summary of protocol amendments

Version number and date	Summary of changes
Protocol v2.0 dated 26 July 2016	• Additional text added to clarify that the primary outcome is disease-free survival measured from randomisation • Addition of outcome 'complications during treatment' • Inclusion criteria, point (3) and point (5iii): 'resectable' amended to 'resectable or ablatable' • Addition of guidance for timing of consent and randomisation of patients with primary colorectal cancer in situ or extrahepatic disease • Inclusion criteria, point (5iii): amendment to confirm that extrahepatic disease needs to be considered curable (instead of resectable or ablatable) • Inclusion criteria, point (5iii): deletion of 'portal vein embolisation' • Exclusion criteria added to clarify that patients need to be suitable for both trial interventions • Guidance added with regard to timing of randomisation for participants with primary cancers in situ or extrahepatic disease

TABLE 1 Summary of protocol amendments (*continued*)

Version number and date	Summary of changes
	• Amended screening data to be able to collect planned treatment for liver metastases in addition to received treatment • Added definition of index disease • Added staging and tumour marker investigations need only to be carried out following completion of successful treatment of the index disease • 'Staging' amended to 'follow-up imaging investigation' • Amended text to reflect that there are no trial-specific screening tests • Added post-treatment CRF will collect data on trial intervention outcome and duration of hospital stay following treatment • Deaths will be reported from randomisation rather than date of consent. Section amended to make clear that expedited reporting of deaths applies to deaths that occur within 6 months of the end of trial treatment • Added liver damage as a post-operative/ablation complication • Refinement of the definition of disease-free survival, specifically with regard to extrahepatic/systemic recurrence
Protocol v3.0 dated 28 February 2017	• Schedule of events amended to reflect that the resource use participant-completed questionnaire is not collected until 3 months post randomisation • Post-treatment care wording amended to read that post-operative care will be as per protocol and not standard practice, as not all sites would conduct CT scans at each of the time points indicated in the protocol
Protocol v4.0 dated 3 November 2017	• Inclusion criterion no 5.0 wording amended as follows (new wording in bold): • Previous wording: 5. Meets ***one or more*** of the following criteria: (i) Considered high risk for surgery due to age (e.g. aged > 75 years) (ii) Major comorbidities as judged by the treating clinician. Examples include history of myocardial infarction, severe chronic airway disease, major cerebrovascular accidents, pulmonary embolism (iii) Liver metastases with poor prognosis or high-risk surgery due to tumour burden. Examples include extensive synchronous disease, need for two-stage resection or ALPPS, small anticipated remnant liver volume, curable extrahepatic disease, down-staged with chemotherapy, poor response after chemotherapy but still resectable or ablatable New wording: **5.** Meets ***at least one*** of the following criteria: (i) Considered high risk for surgery due to age (e.g. aged > **70** years) (ii) Major comorbidities as judged by the treating clinician. Examples include **previous transient ischaemic attack**, major cerebrovascular accidents, myocardial infarction, **severe chronic airway disease,** previous pulmonary embolism, **chronic kidney disease** (iii) Liver metastases with poor prognosis [e.g. requiring down-staging with chemotherapy prior to definitive treatment, poor response after chemotherapy but still resectable and ablatable, curable extrahepatic disease, multiple synchronous metastases, **previous treated lung metastases (resection or ablation)]** (iv) **High-risk surgery** (e.g. needs two-staged resection or ALPPS or portal vein embolisation, small anticipated remnant liver volume) (v) **Recurrence of** CLM **following previous surgery or ablation** • Exclusion criterion 5 – patients who have undergone previous surgery or ablation for CLM – removed • As part of the Informed Consent process, added option to call the participant to discuss the trial and post a copy of the patient information sheet prior to the patient's clinic visit

CRF, case report form.

Randomisation

Participants were randomised by minimisation incorporating a random element (1 : 1 allocation ratio) to either liver resection surgery or thermal ablation (MWA or RFA). Minimisation incorporated a random element, stratified by research site, synchronous/metachronous disease, primary cancer in situ, size of largest tumour, prognostic factors for inclusion, planned surgical resection and planned ablative treatment. Randomisation was performed by the Clinical Trials Research Unit, Leeds.

Interventions

Participants were randomised to either liver resection carried out within regional centres in accordance with individual protocols or thermal ablation, RFA or MWA, depending on local availability and expertise. Centres were permitted to perform ablation laparoscopically or at open surgery if the percutaneous approach was contra-indicated. Minimum ablation and surgical standards were detailed in the LAVA Site Standard Operating Procedures, with ablation criteria based on the CIRSE guidance.[19]

Follow-up

Follow-up of participants was planned at 3, 6, 12, 18 and 24 months post randomisation. All participants were planned to be followed up for 2 years post randomisation. Longer-term survival data were to be obtained from the Office for National Statistics at 5 years post randomisation.

Sample size

A total of 330 patients were required to demonstrate non-inferiority of thermal ablation with respect to resection in terms of the primary end point [2-year disease-free survival (DFS)] with 80% power at the 2.5% one-sided level of significance, assuming a median time to event of 14 months in the resection group and a non-inferiority margin for thermal ablation of 4 months, and allowing for a 5% drop-out rate.

The qualitative substudy had a planned sample size of ≈20 patients, comprising consenters, decliners and those withdrawing post randomisation, and 15 recruiters. Participants were to be recruited from across all centres open during the pilot study. Up to 60 hours of recruitment encounters were to be audio-recorded.

Analysis methods: statistical

Owing to the small sample size and early closure of the trial, it was not possible to perform any of the original planned analysis for the main trial. The intention for the main trial was to assess the difference in DFS. The non-inferiority hypothesis would have been tested using an appropriate survival model to incorporate random effects with respect to research sites, and including adjustment for the stratification factors. Differences in rates, such as complication rates and recurrence rates, would have been analysed using multilevel logistic regression incorporating random effects with respect to research site, and would have included adjustment for the stratification factors.

Analysis methods: qualitative study

In-depth, semistructured telephone and face-to-face interviews were conducted with recruiters (consultants, interventional radiologists and nursing staff), and face-to-face interviews were conducted with patients. Interviews were audio-recorded, transcribed verbatim, anonymised and analysed thematically.[20] This allowed the interpretation of key issues faced by recruiters, and reasons for non-consent from the perspective of patients and staff to be examined. Participant information sessions (recruiter consultation encounters) were audio-recorded (with permission) to examine how information was presented by recruiters and received and understood by patients. An iterative approach to interviewing was taken with earlier interviews guiding later discussions. Data saturation was reached for interviews with recruiters but not with patients because of the small number of patients who consented to be interviewed.

Central scan review

Some of the other objectives of the pilot study were to assess the quality of ablation and the CT scan reporting through a central review. Central review of imaging was carried out for baseline scans, post-ablation scans and 3-month imaging review to assess the consistency between local centre reporting and central review of imaging and whether or not the local centre expertise in ablation was adequate for trial inclusion. The aspects checked in the baseline scans included whether the lesions were unilobar or bilobar, the number of lesions, the size of the lesions, the presence of extrahepatic metastases or extrahepatic nodal involvement, and whether or not the lesions were within the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) criteria. The aspects checked in the post-ablation scans were whether or not complete ablation was achieved in all lesions and whether the treatment margin was ≥ 1 cm or < 1 cm. The aspects checked in the follow-up review scan were locoregional and distant recurrences.

End points

Primary end point

The primary end point was DFS, defined as time from randomisation to the first event, which was defined as any of the following:

- local, regional or extrahepatic/systemic recurrence of disease
- death (any cause).

Local recurrence was defined as the detection of disease at the treatment site after successful trial intervention.

Regional recurrence was defined as detection of disease in the liver – not related to the treatment site – after successful trial intervention.

Extrahepatic/systemic recurrence was defined as detection of 'new disease' at any site other than the liver after successful trial intervention. 'New disease' referred to any extrahepatic/systemic disease that was not already detected before commencement of trial treatment. For example, for participants with primary cancer in situ, detection of that primary cancer after successful trial intervention is not considered to be an 'extrahepatic/systemic recurrence'.

The date of recurrence was defined as the date of the relevant assessment at which the recurrence was detected.

Secondary outcomes

The secondary outcomes included the following:

- overall survival, defined as time from randomisation to death (any cause); to be evaluated at 2 years and 5 years
- local, regional and extrahepatic/systemic recurrence of disease at 2 years post randomisation
- use of subsequent therapies within 2 years post randomisation after treatment failure
- health-related quality of life [EuroQol-5 Dimensions (EQ-5D), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), EORTC Liver Metastases Colorectal Module (LMC21)][21–23] at baseline, and 3, 6, 12, 18 and 24 months post randomisation
- complications during treatment
- post-treatment complications
- length of intensive therapy unit and inpatient stay.

The secondary end points could not be assessed because the trial closed early.

Chapter 3 Results

The trial was measured against 'go/no go' criteria that were set out in the original grant application to achieve a minimum of 15 sites open and to recruit a minimum of 45 participants by the end of the 12-month pilot phase.

Delays during site set-up

The LAVA trial encountered numerous challenges and obstacles that delayed site set-up. These delays were experienced at centres in both the UK and the Netherlands.

Interest in taking part in the trial was high as 12 centres in the UK registered an interest, with a further seven expressions of interest received. However, the target number was 15 sites.

The sites were asked to complete a Site Expression of Interest and Feasibility Form to confirm their eligibility to take part in the trial as defined in the protocol. To be eligible, sites had to meet the research site eligibility and surgeon and radiologist eligibility below.

Research site eligibility:

- The site must be a tertiary liver, pancreatic and biliary (HPB) centre.
- The site must have experience in the provision of liver resection surgery and thermal ablation for CLM.
- The site must have a shared specialised sMDT with representatives from surgery and radiology.

Surgeon and radiologist eligibility:

- To perform liver resections within the trial – prior experience of performing liver resection procedures for a minimum of 20 patients with liver cancer.
- To perform thermal ablation within the trial – prior experience of performing ablative procedures for a minimum of 20 patients with liver cancer.

The sites that met the above criteria were selected and set-up commenced. The trial document packages were circulated to selected sites at the beginning of August 2016. The first UK site opening to recruitment was King's College London on 30 November 2016, but there were significant delays in opening other UK sites for recruitment. It became apparent during site set-up that not all CT scans required for trial assessments were being conducted as part of standard care. There was a delay to site set-up and recruitment while approval was sought from the Research Ethics Committee (REC) and Health Research Authority for exposure to this additional ionising radiation. Following approval of the amendment on 22 March 2017, the first UK site re-opened to recruitment on 28 March 2017 (The Royal Free Hospital, London), followed closely by another four sites in the UK (i.e. King's College London, Cambridge, Oxford and Newcastle).

It was difficult to identify local research infrastructure to support the trial. Links to those with research governance responsibility within the radiology departments and who had a key role in approving the study at the site set-up stage also caused significant delays. Two sites were keen to take part but were delayed because research nurses left, which resulted in a lack of local capacity. Contact was maintained with these sites to facilitate set-up once the local network provided additional support.

Another contributing factor was the radiology approvals. Although the study had received national radiology approval, each department conducted an internal radiology review. This led to further delays in receiving confirmation of capability and capacity from the research and development and hospital finance departments.

At some sites, the trial interventions were delivered across two centres (i.e. surgery in one centre and ablation in the other). This caused delays during set-up while the complexities of the process and accrual allocation were discussed.

Set-up at the sites in the Netherlands also took longer than anticipated. Each site had to submit the study and contract template for review to their local board to obtain approval before they could be open to recruitment. This caused major delays because of contract negotiations and the need to meet Dutch law requirements for participant insurance cover.

Obtaining participant insurance cover that was acceptable to both the sponsor (University College London) and the Dutch REC presented a major obstacle.

Although the UK uses the model non-commercial agreement for research sites in which the main body of the agreement is used without modification or negotiation, this was not the case for the international sites. All changes had to undergo review and negotiation between the sponsor and site lawyers, which took several months as the contract went back and forth between both parties.

As a result of the delays experienced in site set-up and the trial amendment, the pilot phase assessment was reset to calculate the 12-month period from March 2017 until the end of February 2018. During this period, the trial opened in 17 sites (13 UK and 4 Dutch sites).

Screening and recruitment challenges

Owing to the delays in site openings, not all sites were opened for the full duration of the pilot study. Overall, only eight sites were opened for > 6 months during the internal pilot.

Once opened to recruitment, the trial teams at the sites were asked to send screening logs summarising reasons for ineligibility or non-randomisation. We received 366 screening logs for potential LAVA patients from 13 of the 17 sites that had been opened for recruitment. A total of five sites did not contribute any screening data over the course of the study. This includes the site that opened but did not reach the point of screening patients at the time of completion of the pilot.

Of the 366 screened patients with CLM discussed in the sMDT, 59 were eligible (16%) and 307 were ineligible. Of the 59 eligible patients, 14 were not approached, 36 were approached but not consented and nine were consented and randomised.

Of these nine participants, five were randomised to the thermal ablation group and four were randomised to the liver resection group. All but one patient (who was allocated to the thermal ablation group) had metachronous disease, and no patients had their primary colorectal cancer in situ at the time of randomisation.

All of the patients who were allocated to the surgical resection group and three out of the five who were allocated to the thermal ablation group were considered high risk because of their age, and four of the patients allocated to the thermal ablation group had major comorbidities present. No patients were considered high risk because of liver metastases with poor prognosis or high risk for surgery because of tumour burden. In no patient was the largest lesion > 5 cm.

Seven patients completed the allocated intervention. One participant allocated to the thermal ablation group did not receive their allocated intervention because of new clinical findings found prior to the ablation (see *Appendix 2*). Another patient switched from their surgery allocation to ablation as their intraoperative ultrasound showed a more complex anatomical location than previously seen on preoperative imaging. This resulted in the surgeon opting for ablation instead of the planned surgical resection. At 3 months post randomisation, six patients had no hepatic or new extrahepatic disease, one patient had withdrawn, one patient had evidence of new liver and extrahepatic disease and one had not returned their 3-month follow-up form.

Of the screened patients, 16% (59/366) of all patients were considered to be suitable for the LAVA trial. They were appropriate for either ablation or liver resection and were considered to be at high surgical risk because of participant or tumour characteristics. The median age of eligible participants was 75 years.

The trial was stopped early because of poor recruitment as the internal pilot for 1 year recruited only nine participants (UK, $n = 3$; the Netherlands, $n = 6$) out of the recruitment target of 45. No formal statistical analyses will be conducted as there are insufficient patient data to provide any significant conclusions. The health economic analysis will not be performed because of the small numbers of participants who were randomised into the study.

The reasons for ineligibility and non-randomisation can be found in *Tables 2–4*.

Assessing barriers to recruitment and actions taken to increase recruitment

Emerging issues related to recruitment were discussed as some centres reported fewer potentially eligible patients than expected. This was reported to the Independent Steering Committee, which requested that the qualitative team shift the focus of their work from understanding the experiences of patients and staff taking part in the trial to understanding the challenges of identifying eligible patients so that these may be addressed by intervention from the research team.

TABLE 2 Reasons for ineligibility

Reason	Number of patients
Patient not considered high risk	88
Not a suitable candidate for thermal ablation	64
sMDT diagnosis of CLM not considered to be resectable/ablatable with curative intent	43
Not a suitable candidate for liver resection surgery	42
Patient has undergone previous surgery or ablation for CLM	21
Colorectal primary not resected	16
Other	16
Concurrent malignancy	8
Incurable extrahepatic metastasis	2
Patient is taking part in another surgical/ablative trial	2
Planned simultaneous resection of primary and liver metastasis	2
Patient unable to provide informed consent	1
Reason for ineligibility not recorded	2
Total	307

TABLE 3 Reasons for eligible patients not being approached

Reason	Number
Trial closing to recruitment	4
Patient declined treatment	2
Surgeon decision – for ablation only	1
Patient declined surgery	1
Reviewed and proceeding to resection	1
Severe short-term memory loss – for ablation only	1
Patient had treatment preference for surgery	1
Consultant review in outpatient department – proceeding with resection	1
Discussed again at sMDT for ablation referral	1
When reviewed by consultant – lacked capacity	1
Total eligible but not approached	14

TABLE 4 Reasons for patients being eligible but not consented

Reason	Number
Strong preference for ablation	12
Strong preference for surgery	10
Patient did not want to be randomised or had preference (but preference not recorded)	10
Reason for declining not reported	3
sMDT or clinician review and considered unsuitable for liver resection	1
Total eligible but not consented	36

It was reported that there were significantly fewer eligible patients at the sites than expected. Closer examination identified that some sites were misapplying the inclusion and exclusion criteria, and the chief investigator visited each site and met with clinical colleagues to remedy these misunderstandings. Patients suitable for trial inclusion were identified at all sMDT meetings visited. However, this did not lead to improvements in recruitment numbers. Interviews with staff revealed that even when potentially eligible patients were identified in the sMDT meetings, usually chaired by a surgeon, they were often denied the opportunity for discussion of the trial. Few patients consented to be interviewed and so little can be gleaned from their perspective; however, there was some evidence from staff interviews that recruiters struggled to maintain equipoise when presenting the trial.

Prior to study launch, a training manual was developed to help sites with study introduction, and this was discussed at each site initiation meeting. A follow-up teleconference with recruiting staff was also arranged following site set-up to identify early challenges and to go through the training manual with recruiting staff. However, it was many months between training and the identification of potentially eligible patients, so much of the initial learning was lost. During interviews with staff, we explored training needs; however, most centres refused training as they considered that they had a strong track record of recruiting to studies, and so felt that they did not require training. Alternatively, some centres had not identified any eligible patients and so felt that it was premature to judge if additional training were needed.

Thirteen out of the 15 originally planned staff interviews were conducted and these were analysed as intended. The 13 interviews generated 268 minutes of rich audio data. All interviews were transcribed verbatim and managed using NVivo 11 (QSR International, Warrington, UK). The data were analysed using thematic analysis.[20,24] A coding frame was established (MT and JaB) and emerging themes were explored iteratively in the remaining interviews, with additional codes added, and then applied to all transcripts.

The patient recruitment encounters (audio-recordings of recruitment encounters) were examined initially using the Q-QAT (Quanti-Qualitative Appointment Timing) technique[25] to assess the time taken to present each treatment as well as the study itself. Content of the discussion about the surgical and ablation options was then examined, as well as how recruiters demonstrated equipoise and how they described randomisation using thematic analysis.[20] All of the recordings were listened to, detailed notes were made using the Q-QAT technique and then a thematic analysis of the content of the discussions was performed.

Key issues inhibiting recruitment from the perspective of local teams were:

- Fewer than anticipated eligible patients.
- Clinician judgement about the suitability of the patient for both treatments led to fewer than expected patients identified.
- Patient preferences for individual therapies prevented randomisation.
- Lack of a dedicated research nurse for the trial and so inability to attend sMDT meetings and keep the study in the minds of the clinicians.
- Research nurses working across studies and so lacking confidence when talking about the trial or interventions (as few patients approached).
- Fewer than half of the clinicians could recall receiving a training manual, but did not think that they required training to improve recruitment of patients.
- The trial was not well embedded into clinical pathways and so patients had to wait until their second appointment before being consented.

Interviews with clinical staff (both face to face and telephone) were conducted by Jaqueline Birtwistle, an experienced researcher with a background in psychology. Interviewees were consultant surgeons ($n = 5$), a specialist registrar ($n = 1$), an interventional radiologist ($n = 1$), research nurses ($n = 5$) and a research assistant ($n = 1$). All were actively involved in trial delivery and recruitment (*Table 5*).

Clinical buy-in from centres

All of the clinicians interviewed were united in their view that this was an important question that needed answering:

> *I think it is a good question, this trial that's why we agreed to take part.*
>
> *Consultant 2*

However, many acknowledged that the recruitment challenges were greater than anticipated. A few clinicians were surprised that the trial had proven so difficult to recruit to as they were experienced in delivering similar trials, and had well-established infrastructure and processes in place to support trial delivery:

> *We are a large centre, so did not envisage problems recruiting [. . .]. People [staff] were very receptive of the idea of the trial because there is no clear evidence base, especially for high-risk patients. So the sMDT were totally receptive for the trial [. . .] We are a research active centre, we are currently doing three other surgical liver trials [and recruitment is good for those].*
>
> *Consultant 4*

TABLE 5 Staff demographics

Study code/site number	Gender	Age (years)	Role	Ethnicity
Staff1a	Male	55–64	Consultant surgeon (chief investigator)	White Scottish
Staff1b	Male	35–44	Specialist registrar	Indian
Staff1c	Female	[a]	Research nurse	[a]
Staff2	Male	45–54	Consultant surgeon (PI)	White British
Staff2b	Female	45–54	Research nurse	White British
Staff3a	Female	35–44	Research nurse	White British
Staff4	Male	35–44	Consultant surgeon (PI)	Indian
Staff5a	Female	45–54	Research nurse	White British
Staff6	Male	45–54	Consultant surgeon (PI)	British Asian
Staff7	Male	[a]	Research nurse	[a]
Staff8a	Male	[a]	Consultant surgeon	White Scottish
Staff8b	Male	55–64	Consultant interventional radiologist (PI)	White Scottish
Staff8c	Female	45–54	Research assistant (college training)	White British

a Declined to provide data.

Local investigators described how they had actively promoted the trial to colleagues to ensure that teams were aware of it, but acknowledged that clinical equipoise among some colleagues was low and that this hindered engagement. They described how some colleagues were reluctant to engage with a trial that they perceived to be difficult to recruit to. Despite regular presentations about the trial, misconceptions about the eligibility criteria were commonly reported and this may have fuelled a lack of clinical buy-in:

> *They all [consultants] know about the trial because I have presented here twice, some of them I think will get involved with the trial once we've got it up and running and ironed out any difficulties. Some I suspect will not wish to get involved. [. . .] Some surgeons don't believe that there is any uncertainty, that surgery is the best treatment, they're quite adamant that it is and that there is no doubt, they don't have any doubts, there is no doubt in the literature, and if they don't have any doubts about what the right treatment is. I don't think they are going to be able to discuss the trial.*
>
> *Consultant 1a*

> *The nurses were repeatedly asking me 'So, can we, can we actually consider on this trial for someone younger than that age?' and so on. They were under the misconception that people had to be 75, or 70 whatever, and we could only recruit patients of that age, so that was a major misconception.*
>
> *Consultant 1a*

When confusion about the eligibility criteria was identified, the chief investigator set up site visits and attendance and presentations at centre sMDT meetings. Regular recruitment forum meetings took place to share good practice and discuss recruitment challenges.

Are there enough eligible high-risk patients?

Opinion was strongly divided on the question of whether or not there were sufficient eligible patients for this trial. Some surgeons believed that the inclusion criteria meant that there were few eligible patients, whereas others maintained that eligible patients exist and used their own records to support

this, but believed that clinician preferences meant that suitable patients were not being considered, or were being excluded by the sMDT, which was usually chaired by a surgeon:

> *No I just don't think there's enough patients.*
>
> *Consultant 2*

> *I think the numbers you've got are actually quite small, who would be appropriate, and then, yes, and then there's the issue of equipoise amongst the clinicians that again cuts it down even further.*
>
> *Consultant 6*

> *We went through our sMDT minutes for last year to estimate the number of potential patients we would have, so I was thinking roughly 15 to 20 a year who would be eligible, and I thought they would be straight-forwardly accepting to go on the trial. I was wrong.*
>
> *Consultant 4*

One of the biggest challenges from the perspective of recruiters was the involvement of the sMDT, usually chaired by a surgeon, in screening eligible participants. Conflicting views about the eligibility criteria and clinician preferences meant that eligible patients were excluded from the trial. The role of the sMDT in the LAVA trial was to determine patient eligibility, and recruiters described how some colleagues acted as gatekeepers, screening outpatients who the participating clinicians believed would be good candidates. The dominant discourse was that, if the surgeon caring for the patient did not feel that the patient would benefit from trial involvement, then the patient was not provided with trial information or an opportunity to discuss the trial. There was a strongly held view by local PIs that many colleagues believe that surgery is better than ablation, and 'their fragile equipoise evaporated when faced with individual cases', making it difficult to get patients through the sMDT. Two surgeons also made the case that a surgeon is rated on their ability to undertake complex surgeries, so there is a strong preference for surgery and an imperative to undertake complex cases:

> *I think we've all slightly been taken by surprise by the fact that in many instances in the sMDT, when a patient is considered to be a potential candidate we find that for one reason or another, there is a very clear preference for one treatment over the other. [There is] a strong feeling that there isn't equipoise in the treatment option, so ethically we don't feel if it was for ourselves or a relative, we just don't feel that offering the trial is acceptable, and that's happening more frequently I think than we anticipated.*
>
> *Consultant 2*

> *Surgeons are not rated on their ability to cure patients, surgeons are rated on their ability to perform more complex operations. So ultimately the more complex operations that you perform technically well – the better surgeon you are – that's what people consider.*
>
> *Registrar 1b*

In interviews, some put clinician reluctance to put patients forward for the trial down to a difference in the threshold for surgery between surgeons. Other common reasons for refusing to put patients forward were a belief that the tumour was inoperable and a belief that the patient would not want to take part, so there was no point in offering the trial:

> *. . . today's patient, both myself and [interventional radiologist] would have been perfectly happy to randomise, but the colleague whose patient it was felt that they had a preference for ablation, and that can be a problem because where equipoise lays varies between consultants, so the main problem is finding patients. Everybody in the sMDT is screened for LAVA, we just, we have that as a routine, for every single patient, and we don't really miss any, so it's about equipoise in the staff in the senior staff about whether they are or are not suitable for LAVA.*
>
> *Consultant 8a*

Clinical equipoise

Most clinicians had seen few eligible patients at time of interview. Only two clinicians provided audio-recordings of the consultation or recruitment interview, so evidence of how the trial was presented to patients is very limited. The audio-recordings were from consultants who had attended the recruitment training, were involved in the study design and were very experienced in presenting studies to patients. The recordings showed that these recruiters had a generally good understanding of how to present the trial in a balanced way. Although the discussion was driven by the clinician, the terminology used did not overtly favour one treatment over the other. Both clinicians took time to check the patients' understanding of the treatment options in the trial and answered questions as they went along. However, neither actively challenged patient preferences when these were expressed.

In the interviews, we asked clinicians about equipoise in the clinical community, and found that although clinicians felt that at a community level there was equipoise, clinicians found themselves not to be in equipoise when faced with individual patients:

> *He [surgeon] pushed the patient towards ablation and not in for randomisation, he just said 'comorbidities are against resection here' and pushed that particular patient towards ablation.*
>
> *Interventional radiologist 8b*

> *I think as a whole, the whole HPB surgery community probably rather underestimated the number of times where there actually isn't equipoise, I think that's what I perceive as a main issue.*
>
> *Consultant 2a*

We asked clinicians to run through what a recruitment encounter might look like. All said that they would start by discussing the diagnosis with the patient before introducing the trial. The trial would be mentioned mid-way through the appointment, but not discussed in detail until after the treatment options had been presented. When asked about their own treatment biases, all mentioned that they felt comfortable saying that they did not know which treatment was best, because they had the opinion of the sMDT to back up this decision. If the sMDT thought that the patient was suitable for the trial, the consensus was that the participating surgeon should be in equipoise, because the sMDT was in equipoise:

> *I do a lot of randomised trials so I would hope that if there is true equipoise such that we've decided to offer them the trial, they would not for me pick up bias because essentially I wouldn't have it, I wouldn't be asking them to participate.*
>
> *Consultant 8a*

Although many surgeons claimed to be in equipoise, the terminology used in the research interviews indicated that there was often some unconscious bias towards surgery, with surgeons often presenting surgery first, and describing it more positively than ablation. Surgery was described as 'standard treatment' and, although it was common for the risks of surgery to be clearly described, the risk of cancer recurrence was mentioned less often. In contrast, ablation was described in a balanced way, or recruiters expressed less confidence in the treatment:

> *If you say well you know, the results from ablation have never been proven, you know, effectively compared to surgery then they say 'well why would I want to have something that's inferior?'.*
>
> *Consultant 6*

> *I would say to the patient that in our practice of standard care in the absence of the trial, it's surgical resection, that is our policy. In someone in whom both treatments could be done unless there's a specific*

> *reason for them to have ablation, and that would be either related to prior surgery or related to their poor state of health, in general terms they would be offered surgical treatment in the absence of the trial.*
>
> *Consultant 8a*

When asked, clinicians admitted that if a patient asked for their professional opinion they would still guide the patient towards surgery, and the interventional radiologist and nurses also believed that this would be the case:

> *The feeling among the surgeons, be it correct or incorrect, or evidence based or not, is that surgery is preferential. And so, if the patient asks the surgeon, which they quite often do, you know, 'what would you do?' or 'what would you do it if it was your mother or father?'. And they will, they do all prefer surgery.*
>
> *Nurse 3a*

Both clinicians and nurses talked about the complexity of the decisions patients needed to make, and the importance of ensuring that patients understand their choices. This complexity could have an impact on how the trial was presented, the order in which information was discussed, and whether or not the study was presented at all:

> *I would talk them through what the procedures would involve. Then I would explain the question of equipoise, of uncertainty as to which, whether or not one or other treatment is better, and then I would try and work out whether or not the patient understood the question about the different treatment options and how there might be uncertainty as to whether or not one is better or worse. If I thought they had understood that question, that there might be two treatments that are similar with some advantages and some disadvantages to both arms, then I would now introduce the concept of the trial.*
>
> *Consultant 1a*

> *. . . equivalent ablation might be a percutaneous one, so what that means is that in counselling the patients about the two options although from a cancer perspective the two may be equivalent, from a post-operative recovery perspective it's very different.*
>
> *Consultant 2a*

Three clinicians sought to reduce the variability in how the trial was presented by seeing all potentially eligible patients themselves. However, this had unexpected negative consequences for the clinician involved because many of the patients did not prove to be suitable for the trial.

> Participant: *. . . that group of high-risks patients are all seeing me which is maybe a disadvantage but maybe from a point of view of trying to get the trial running it's ideal.*
>
> Interviewer: *So, what makes it a disadvantage?*
>
> Participant: *Well I've got operating lists to fill and if I see only the patients that are extremely high risk, I spend the vast amount of my clinic time seeing patients that may not have surgical treatment – so, in a way, it's just practical difficulties.*
>
> *Consultant 1*

What is patient acceptability of the trial?

Of the four patients initially consenting to interview, two subsequently declined for health reasons. Both interviewees were decliners. One patient thought that their clinician was able to maintain a good level of equipoise, but the other reported that, when asked, the clinician had expressed a preference for ablation, 'in her case'.

Mrs A: decliner

Mrs A was a woman with close family members in the medical profession. Her account of being told about the study suggests that the information given was clear; she understood the rationale for the study and easily described the advantages and disadvantages of each treatment option. Her surgeon explained what randomisation would mean, and during the interview she was adamant that she had not wanted to participate in the study because she wanted to choose for herself, although, in reality, she sought advice from her surgeon and subsequently accepted his suggestion:

> Mrs A: *He explained there was a trial going on where they would assign you to either or and I said I didn't want that, I wanted to choose myself [. . .] I didn't want to be included – I know what they are doing it for, to see if there's . . . if there's a better way, which is the better way of doing things.*
>
> *I asked him straight out, what would you do? He said well if you were my mother I'd go for the ablation.*
>
> Interviewer: *OK, so he favoured the ablation?*
>
> Mrs A: *No he didn't favour it, but he said that is what I would do if I was his mother.*

The patient had strong clinical reasons to decline surgery, and so whether or not she accepted the advice of her surgeon because it accorded with her own views is unknown.

> *I've already had several major operations on my bowels, because I've had colon cancer, I've had, my abdomen looks a bit like a criss-cross now, noughts and crosses, so I don't want any more if I can help it [. . .] every time you have major surgery you run the risk of adhesions, I've had palpitations in the past and they are not very good.*

Mr B: decliner

Mr B was an elderly man who lived > 80 miles from hospital. From Mr B's perspective, involvement in the study meant that his doctor could not apply their clinical judgement to advise him which treatment was best for him, a position that Mr B found intolerable. In the face of uncertainty around the treatment options, Mr B sought evidence from the internet to support his preferred choice. Although his clinician took the time to explain the difficulties of his preferred treatment option, the patient did not want to return to clinic for additional treatments, and so declined the trial:

> *Yes he [surgeon] went out of his way to try and keep it [balanced] . . . but I am well educated and intelligent and I very easily found out which was the preferred option, in my particular case, surgery, so I'll be having that. I felt that they were taking away that option from the guy who was a consultant and your specialist and that if he felt that your best option was either one he didn't really have the choice of saying well that's the one we want to give you.*
>
> *[Consultant] went out of his way to be neutral about everything, but as I said, my own research said that the only absolute certain way as far as liver surgery is concerned providing it's not more than one [tumour] and providing the position and all the rest of it, bearing in mind the liver can repair itself after it's being operated on, I felt quite strongly that it had to be surgery because I didn't want to be left with having to go back, and go back and go back.*

Understanding and addressing patient preferences

At the time of their interview, four out of five surgeons had identified and approached at least one eligible patient. There was a strong belief among all of them that patient preferences existed and recruiting staff reported that they did not feel comfortable challenging patient preferences. For this reason, telephone-based training using a six-step recruitment process to help direct discussions[17] had

been provided to all sites to help them present the trial in a balanced way and to help them gently probe patient preferences. However, delays in opening sites meant that several months had passed before they approached any eligible patients. This meant that the learning accrued during the training had been lost.

Patient decision-making is known to be affected by the initial clinician encounter, and there was a belief that preferences were often already set before the patient met the liver team. Referrals came from colorectal colleagues, often based in other hospitals, and almost all of the clinicians mentioned that patients had already been made aware that they had been referred for surgery (rather than to discuss treatment). The surgeons felt that this made it difficult for them to introduce the possibility of the two different treatments in the study and proposed that communication with referring sites needed to be improved:

> *We do find sometimes that the treating clinicians before referring to us haven't actually explained everything, you know, or imply the surgery is something very minor without risk you just cut here. [. . .] So they don't go in to the depths, we kind of start afresh pretty much, making sure they understand the diagnosis, the prognosis, the treatment options, the complications, risks, etc.*
>
> *Consultant 6*

A further complication was that patients were coming to see a surgeon at a surgical clinic, which primed patients for discussion of surgical intervention. A key patient eligibility criterion was 'high risk for surgery', but most patients had already undergone surgery for their colorectal cancer, and interviewees at one site reported that many patients they met with could not reconcile themselves to the idea that they were high risk:

> *You're talking about a non-surgical intervention in a surgical clinic, and patients know they're coming to see a surgeon, and surgery has been mentioned to them all along their investigations. These are patients with metastatic disease so therefore they've already undergone surgery for bowel cancer, they know the drill, [. . .] if they've undergone a bowel operation then to them they're fit for a liver operation.*
>
> *Nurse 5a*

> *The problem with the referring hospitals is they don't necessarily have the expertise to know the options. Usually when they refer patients in they refer them in to a liver surgical clinic, so the patient expects liver surgery.*
>
> *Consultant 5*

Staff interviewees described how some patients were adamant they did not want further surgery if they could avoid it:

> *Most of our patients have had a bowel operation and chemotherapy and have had enough of surgery. They prefer ablation. They know they can always come back and we will take it [cancer] out. That is a plan for them as well, this way they can have a better quality of life. [. . .] They keep coming with such strong opinions of their own, which is very, very unusual in our region, we are very surprised it happened. As we do so many trials, they come mentally prepared for that, most of them are, which is why I was so taken aback when a patient said, 'No, I want RFA'.*
>
> *Consultant 4*

Clinicians also described how, in other cases, patients came to their first appointment with strong preferences, and these were often based on personal situation as much as clinical factors:

> *It depends quite a lot actually on their social situation and so people that might have a lot of caring responsibilities or they want to get back . . . you know perhaps to work or something like that, they all really prefer ablation. People that are perhaps looking at the longer-term benefits, then they're quite, you know they're not worried by surgery. That sort of thing, they, they tend to go for surgery.*
>
> *Nurse 3*

Although recruiters did ask patients why they had a particular preference, they tended to accept the reasons given at face value if these preferences appeared informed in the light of the patient's own circumstances:

> *I am uncomfortable doing that [challenging preferences], for example because according to, let's say the Helsinki declaration if they have a strong preference then their interests go ahead of any other interests.*
>
> *Specialist registrar 1b*

> *All of the ones that I've seen have very quickly said 'I would prefer . . . one or the other'.*
>
> *Consultant 3*

A common discourse from nurses was that they were reluctant to challenge patient preferences, arguing that it was not their role to coerce patients into taking part in the trial:

> *We got another lady and she preferred ablation because [. . .] She was going to have, go for surgery eventually. But she was treating the liver lesions first and so . . . she didn't want two surgeries – one for the liver and one for the colorectal afterwards, so she preferred ablation [. . .] they consider their situation, what they can bear I think . . . that would fit within their lives.*
>
> *Nurse 1c*

In contrast, when patients expressed misconceptions about the two treatments, staff felt able to manage these much more easily, as such misconceptions are common in clinical practice:

> *I think the fact that they've all been discussed at the sMDT before we see them in clinic helps because we can back our discussion up with the fact that it's been discussed by a group of experts. I don't think that's an issue as much for us. Now there may be some misconceptions about the technical aspects of ablation or the surgery or whatever, and that's something we can address.*
>
> *Consultant 6*

> *To get anything out of a consultation they need to be in complete understanding of the facts [. . .] and so I am happy, if they have a misconception, then I'll say, 'well, it might not be like that . . .' and explain and give them the evidence and the facts. I would never let anyone walk out of the room with a misunderstanding or they will base their choices on that.*
>
> *Nurse 3a*

Integration of the trial into clinical practice

The study was not well integrated into clinical practice and some recruiters felt that the structure of the recruitment process was weighted against recruitment. Recruiters described how some patients appeared open to the study initially, but changed their mind by the second appointment. The study and the issue of clinical uncertainty were introduced to patients during the first meeting. In the face of this uncertainty, patients used the time between appointments to decide which treatment was best for them, often talking to family and friends, and returned to the second appointment having made a treatment decision:

> *In one case the patient had made up their mind they wanted surgery and they wouldn't countenance ablation, and the reverse was another case, you know, so it is difficult.*
>
> *Consultant 6*

Some centres thought that recruitment would improve if this criterion was changed, which was a view that was not universally supported because others felt that the information provided was too complex for one visit:

> *The problem was the consenting procedure. The protocol had the patient returning to clinic a week later, and that was a problem as patients travel a great distance. This was amended, so now we see them the same way we do other trial patients, we see them once and give them the information sheet and then they post it back to us, if they consent. [. . .] most patients are receptive to trials here, we are a very research-oriented institute and we have not had any problems with other research we have. When people come here, they know they are going to be asked about trials.*
>
> *Consultant 4*

> *To explain the complexities of the differences and give them time to take that on board and then introduce all the issues about different treatment options and all the pros and cons of the different treatments, it is a lot to take on board. [. . .] How somebody that has just been introduced to this [trial] could possibly take it all on board, I think it is a lot and as you know some of the centres are saying well let's do it in just in one visit, and I don't know.*
>
> *Consultant 1a*

A further problem with the recruitment process is that patients did not get to see the interventional radiologist until the surgeon had seen the patient, and so some patients were screened out before the interventional radiologist got to see them:

> *I'm not seeing the patients, the surgeon is, and therein lays a problem, possibly on some sites, you know, it's, it remains the historical case that the surgeon sees them in outpatient clinic when the trial is really of ablation [. . .] so there is a lack of a balanced process.*
>
> *Interventional radiologist 8b*

All nurses worked over multiple trials and some reported a lack of experience when talking about trial options with markedly different interventions and acknowledged that they still needed time to get to know the project. Familiarity with the trial was hindered by the small numbers of patients being approached, as nurses did not get to sit in on consultations and so improve their knowledge through regular and repeated exposure to discussions about the interventions:

> *I don't know much about the ablation to be honest, and that something I think as part of the study that we're learning as we go, because the pathway for patients is different [. . .] that's something we are trying to get our heads around as well.*
>
> *Nurse 5a*

Patient and public involvement input to the LAVA trial

The PPI representative in the Trial Management Group was actively involved during the grant application stage of the trial. The input and guidance received for the patient information was valuable during early trial development. However, once the trial moved to the set-up and recruitment stage, it was difficult to allocate a specific task to the PPI representative as there were only a few patients recruited to the trial. We met with the PPI representative to discuss where their input would be more valuable. A plan was put in place for the PPI representative to assist with the qualitative study, review the patient recruitment encounters and discuss the patient interviews. Unfortunately, this was not achieved as the PPI representative had to resign because of poor health.

Computed tomography scan central review

Baseline review was carried out on six patients. There was consistency between local centre reporting and central review as to whether the lesions were unilobar or bilobar and as to the number of lesions. The segments were consistent in three patients, over two segments rather than one in two patients and in segment 5 rather than segment 6 in one patient. The difference in the size of the lesions varied from 2 mm to 6 mm and was not available for two lesions. There was no extrahepatic nodal involvement noted in either the local or the central review. In one patient, a lung metastasis was noted on central review and not on the local team report.

Central review showed minimal size differences in the lesions, all of which were within CIRSE criteria. The stage of the disease was considered different at central review (possible lung metastasis) in one patient only.

Post-treatment scan

Central review of the post-treatment images suggested that there was complete ablation of all of the lesions, as suggested by local team reports. The treatment margin was > 1 cm in three out of the six lesions but was felt to be < 1 cm in the other three. Overall central review supported local centre assessment of successful treatment.

The scan review suggested that all local centre expertise was appropriate.

Three-month follow-up

The 3-month follow-up scan was available for five patients. One patient had developed liver recurrence and two developed lung metastases.

Central review raised uncertainty as to whether or not the patient with a 5-mm lung metastasis had metastatic disease. CT scanning has a low diagnostic accuracy for small and solitary lung lesions and serial review would be required to confirm or refute this finding.

The follow-up imaging review supported local review in all except one patient, for whom follow-up imaging would be required for a definitive result regarding the presence or absence of recurrence. Therefore, differences are minor and suggest a high standard of local team radiology reporting.

Chapter 4 Discussion

Main trial

We have reported the results of the internal pilot of a RCT comparing liver resection surgery with thermal ablation for people with CLM and who are considered high risk because of patient or tumour characteristics. We have highlighted the difficulty in recruiting into a RCT of this nature and the reasons for non-randomisation.

The delays in site set-up during the 1-year pilot led to reduced opportunities for recruitment despite our efforts to reduce the site opening times. In addition, the screening data received showed that only 16% of patients with CLM were eligible for the trial. The lack of a uniform definition of high surgical risk may have been a problem for identifying suitable patients at the sMDT meetings.

The lack of equipoise at site, patient preference for either ablation or surgery, and the dislike of randomisation were the main reasons for non-randomisation. It should be noted, however, that there was no evidence that more patients preferred ablation over surgery or vice versa.

Although hypothesis testing was considered to be inappropriate because neither the hypothesis nor the sample sizes were calculated a priori, the numbers of participants who expressed a strong preference for surgery or a strong preference for ablation were quite similar. This is surprising given that surgeons might be predicted to have a bias towards liver resection even in those who are high risk.

Qualitative study

During interviews with clinicians, they all described episodes where fellow members of the sMDT, usually chaired by a surgeon, declined to provide information on the trial for suitable patients or to allow patients an opportunity for trial discussion. This resulted in fewer than one-third of patients who fulfilled the criteria for the trial having a face-to-face discussion about recruitment into the LAVA trial. One solution would have been to screen referred patients and highlight their suitability for the trial prior to a discussion at the sMDT meetings.

Trial eligibility criteria involved the application of clinical judgement, and surgeons tended to view patients simply as having resectable metastases, or not, rather than weighing up the option of two treatment modalities.

The original idea behind this study was to identify those patients who were at high risk physiologically or oncologically. Several interviewees acknowledged that some surgical colleagues did not have a good grasp of the clinical research evidence and so were convinced that surgery was better than ablation and, therefore, were reluctant to have their patients involved in the trial. If patients were at high risk physiologically for surgery, the risk of mortality was higher. This led some clinicians to ask 'Why would I even randomise this patient? They are too high risk for surgery, I would send them for ablation'.

With a few exceptions, centres also cited a lack of suitable patients as a major reason for poor recruitment. One centre had compared its anticipated numbers with its actual number of eligible patients but could not find an explanation for the lower than expected numbers. The difference in numbers of patients screened (screening log data) suggests that some sites had difficulty with clinical equipoise and so did not screen some patients. Surgical trials are known to be difficult to recruit to[26–28]

and, for this reason, time was dedicated during site set-up to train trial staff about recruiting and the importance of having clinical equipoise. However, the sMDT, usually chaired by a surgeon, many of whom were not actively involved or supportive of the trial, made this training process less effective, as these clinicians did not take part in training. The findings of the study suggest that the LAVA trial suffered from a lack of clinical equipoise at the community level. Although all of the local PIs wanted the trial to succeed, the role of the sMDT in clinical decision-making undermined the equipoise necessary for the LAVA trial and reduced any influence that the local PIs had over trial recruitment. More time and input was needed at site set-up to get referring centres and all members of the sMDT on board for the trial, and ensure that staff understand, and buy into, the rationale for the trial. Basic training on the importance of equipoise was delivered at the study launch and site initiation meetings, but this was not disseminated to the many members of the sMDT. A manual was also provided with a six-step recruitment plan to help guide discussions with patients. However, this training focused on how to present the trial to patients in a balanced way. It did not consider how to educate the sMDT members and ensure equipoise within the wider clinical community.

There is some evidence from interviews with patients and staff that clinicians did not always present the interventions in a balanced way, with surgery often painted in a more positive light than ablation, and the risks of cancer recurrence after surgery were not always mentioned in the consultation episode. Such biases were anticipated and a series of learning opportunities were built into the study to address this. The chief investigator gave a presentation of the research evidence at the study launch, and repeated this information in the study protocol, at site initiation meetings and as centre sMDT attendances. However, in most sites several months elapsed between site initiation and first patient being approached, and learning accrued from exposure to the research evidence was potentially lost. It may also be the case that the clinicians were not convinced by the evidence and training did not change long-held views. The site leads, who were engaged and may have been well informed regarding the equipoise in the patient group to be recruited, were small in number compared with the many members of the sMDT who may have lacked understanding of the background evidence and hence may have been disinclined to support recruitment.

Similarly, some of the nursing staff involved in recruitment lacked confidence in describing the two treatments, and this may also have contributed to poor recruitment. Interview data from across the sites suggest that the structure of the recruitment process had the potential to introduce a bias towards surgery as ‘a patient seeing a surgeon expects surgery’. Although this was a trial of ablation, there was no interventional radiologist input at the recruitment interview, and the interventional radiologist did not appear well engaged at most sites, as evidenced by the fact that only one interventional radiologist agreed to be interviewed. This may have biased some patients away from the trial as they did not know enough about ablation to make an informed decision.

There is significant research evidence to show that the informed consent process is a point at which many patients are lost to surgical trials.[29] To mitigate this, the current study provided training on how to present the trial and interventions in a balanced way. The written information provided details of a technique that had worked in previous clinical trials, but many interviewees were unaware of the manual, and most refused additional training because at the time of the interview they believed themselves to be competent recruiters or had still not approached a patient. We also planned to record recruitment encounters to monitor discussions about the interventions and study processes to identify good practice and areas where support was needed. However, despite multiple reminders, recordings were received from only two clinicians. These recordings provided no evidence of systematic bias in describing the trial or interventions to patients, but both were experienced researchers.

Our ability to develop a strong plan of action to improve recruitment was hampered by a lack of data. We were able to interview only six surgeons who were involved in recruiting to the trial from 13 UK sites, and received details of only four potential UK patients to interview. This limited our ability to fully comprehend the challenges to the recruitment process at all sites. Aspects of the Quintet Recruitment

Intervention[30] were embedded into the pilot study, specifically interviews with recruiting staff and audio-recordings of appointments between recruiters and potentially eligible patients. However, if we had undertaken interviews with staff prior to the study opening, we may have identified some of the hidden challenges to recruitment, in particular the influence of the sMDT in decision-making and the misconceptions about the trial inclusion and exclusion criteria, which we could have addressed prior to sites opening. Similarly, if we had undertaken a feasibility study, we would have been better placed to revise our study protocol to address the issues identified. Owing to funding considerations, a decision was taken not to undertake recruitment training at sites during the pilot study and, with hindsight, the difficulties that recruiters experienced with challenging patient preferences could have been addressed if staff had received explicit training to do this.[27]

Chapter 5 Conclusion

Despite the pilot study not progressing to a full trial, the internal pilot study was successful: it identified that this type of trial could not be run in the existing set-up and facilitated the correct decision being made to stop the trial. Several lessons were learned from trying to set up and run this type of surgical trial. This type of study comparing two very different treatment modalities could have benefited from a feasibility study to provide a better estimate of the number of participants eligible for the trial and iron out any misconceptions about participant eligibility. However, such a feasibility study should be a feasibility RCT as many of the issues related to equipoise would not have been identified in a feasibility observational study. In the absence of a randomised feasibility study, a longer and more intensive phase of internal pilot study would be required in trials of this nature to resolve the issues. This might be in the form of training to avoid unconscious bias of the recruiters and training the clinicians who make the referral, so that the patient does not come with a preconceived idea of what form of treatment to expect. The importance of having resources in place to permit set-up within a reasonable time frame was evident and critical to a trial with a milestone of recruitment in a pilot phase within a short time period. If highlighted by sites at an early stage, this can be addressed and supported in the UK via the NIHR Research Networks, where appropriate. It is probably prohibitively expensive to have dedicated trial staff for a trial of this nature with an anticipated recruitment rate of four or five participants per centre per year. However, having resources available at the time of recruitment through NIHR Research Networks can facilitate recruitment, and sufficient time should be allowed for making these arrangements.

Once site set-up has been achieved, the issue of buy-in at centres (particularly the sMDT) needs to be addressed. This was critical to the screening and approaching of potential patients. In this trial, we attempted to obtain buy-in by visiting all recruiting centres' sMDTs and giving presentations on the trial background and helping to identify potential patients. Recruitment did improve following site visits and the number of potentially eligible patients increased. However, these eligible patients were not always converted into recruits because of the perceived lack of equipoise.

We have highlighted that the lack of equipoise among some of the site personnel and patients did hamper recruitment efforts. Therefore, we would recommend that similar studies have a robust process in place to address any signs of lack of 'equipoise'.

The challenge in including PPI representatives in research is keeping them actively involved throughout the different stages in the trial. This was achieved at the grant stages for the trial, which was a busy period with lots of activity around patient information development. However, when the trial entered site set-up phase, the activity and discussion was focused around reducing trial set-up time and recruitment. There was little input from the PPI representatives and they felt that they should have been more involved. We would have probably benefited from a plan of how they would contribute to the trial at the different stages and have this agreed with them at the start of the trial.

Lessons for the future

From the above discussion, it is evident that the uncertainty about the relative benefits and harms of thermal ablation versus liver resection in high surgical risk patients with CLM will remain for the next decade.

Surgeons and other members of the sMDT should be aware of the ongoing lack of evidence to guide the choice of liver resection or thermal ablation in patients with colorectal liver metastases, especially in those who are in a high surgical risk group. A change in current clinical practice may be necessary. It would be good practice for treating clinicians to provide detailed information about the uncertainty

that surrounds the issue including the risks of the interventions and the success of cancer eradication while considering patient preferences.

If we were to set up the LAVA study again, we would ideally conduct interviews with the entire sMDT at each centre before the trial began and identify how we could better integrate the trial into clinical practice, as many of the challenges identified during the pilot study could have been addressed if they had been more clearly understood at an earlier stage. Similarly, earlier patient engagement to understand why many patients had a strong treatment preference despite a lack of evidence to support individual treatments could have helped to develop clinician expertise in understanding and questioning patient preferences. This would also have allowed us to explore possible patient preferences for treatment, and if we had widened the PPI group to incorporate more members we may also have picked this message up from them.

The use of the sMDT to identify eligible patients highlights the importance of getting the whole clinical team on board, and indeed ensuring that patients feeding into the trial have not been primed to receive surgery. We would undertake more intensive work with sites prior to opening to ensure that they understand the trial and that the entire sMDT is supportive.

The pathway for patients through the eligibility assessment and consent was complex. The need for a second visit to determine eligibility for ablation meant that many patients were lost to the study. We would work with centres more closely to see if there are ways of simplifying this process. We would also explore the feasibility of either training nursing staff to counsel and recruit patients or having both a surgeon and an interventional radiologist present when discussing the two interventions.

At the point that sites opened to recruitment we would undertake face-to-face training at each site with recruiters to give them experience of exploring patient preferences. Recruiters were often content to accept these at face value, if they appeared 'sensible', and so missed opportunities to engage with the patient in a discussion about the study.

Although we incorporated some aspects of the Quintet Recruitment Intervention approach into the pilot study, this was not well supported by sites and so its usefulness was curtailed. In future, we would ensure that all sites agreed to support the efforts to optimise the recruitment process. Finally, as recruitment at the Dutch sites was better than at the UK sites, with hindsight it would have been informative if we had gained ethics approval to undertake interviews with international colleagues to see if lessons could be learned from their experience.

These lessons are applicable in multicentre RCTs comparing major surgery with non-surgical treatments where the anticipated number of eligible patients per centre is low. It is also useful to get regulatory approvals for qualitative research in other countries in international multicentre RCTs to gain insight into the way that trials are conducted in different countries with a view to increase UK trial recruitment.

Conclusions

The uncertainty remains about the relative benefits and harms of thermal ablation versus liver resection in high surgical risk patients with CLM. Surgeons and other members of the sMDT should be aware of the ongoing lack of evidence to guide the choice of liver resection or thermal ablation in patients with CLM, especially in those who are in a high surgical risk group.

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Johannes HW de Wilt (https://orcid.org/0000-0001-6773-9668) (Colorectal Surgeon) participated in the study design, was part of the team that secured the funding and commented on the manuscript.

All authors read and approved the final manuscript.

Data-sharing statement

The major aspect of this study is a qualitative study and, therefore, the data generated are not suitable for sharing beyond those contained within the report. Further information can be obtained from the corresponding author.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Trial schema

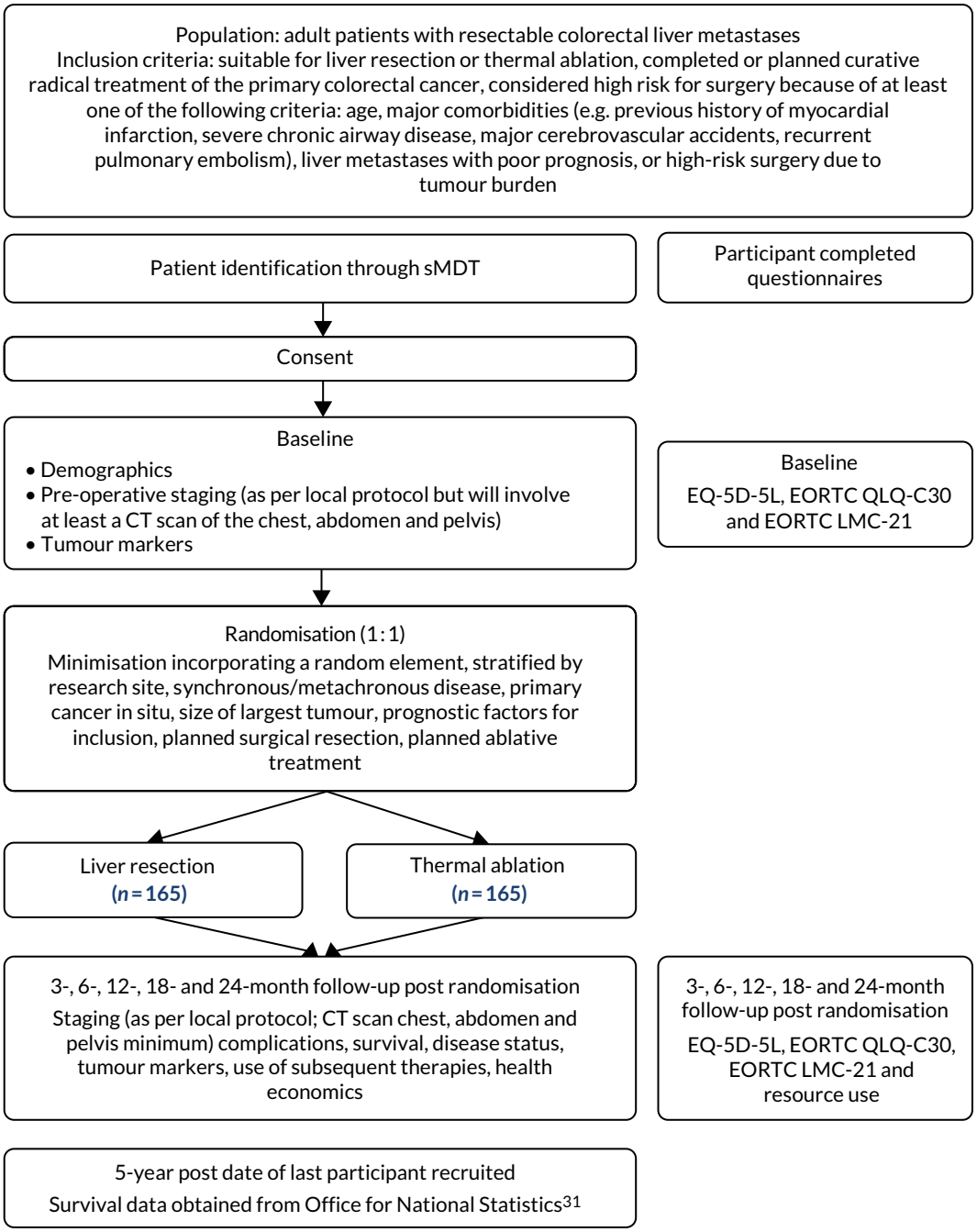

FIGURE 1 Trial schema.

Appendix 2 Participant flow diagram

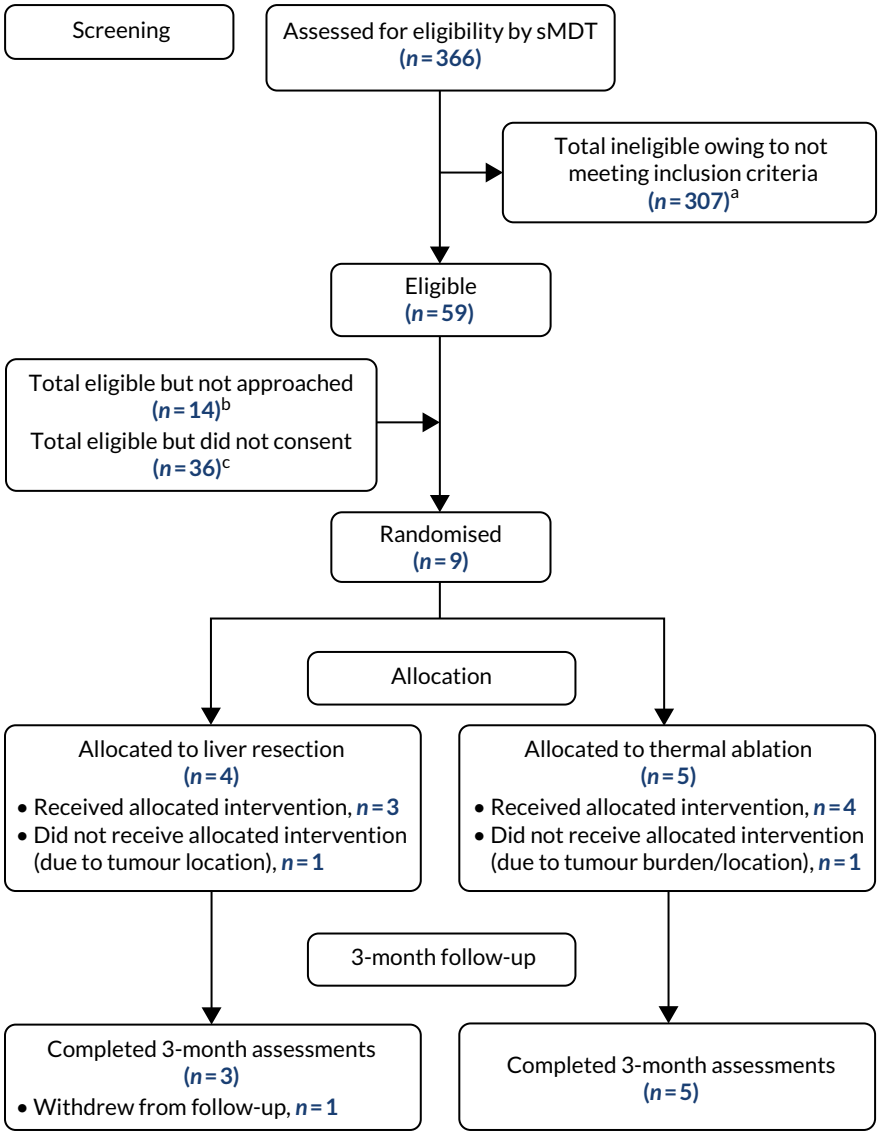

FIGURE 2 Participant flow diagram. a, See *Table 2*; b, see *Table 3*; and c, see *Table 4*.

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