Liver resection surgery vs. thermal Ablation for colorectal liVer metAstases

LAVA

Liver Resection Surgery Versus Thermal Ablation for Colorectal LiVer MetAstases

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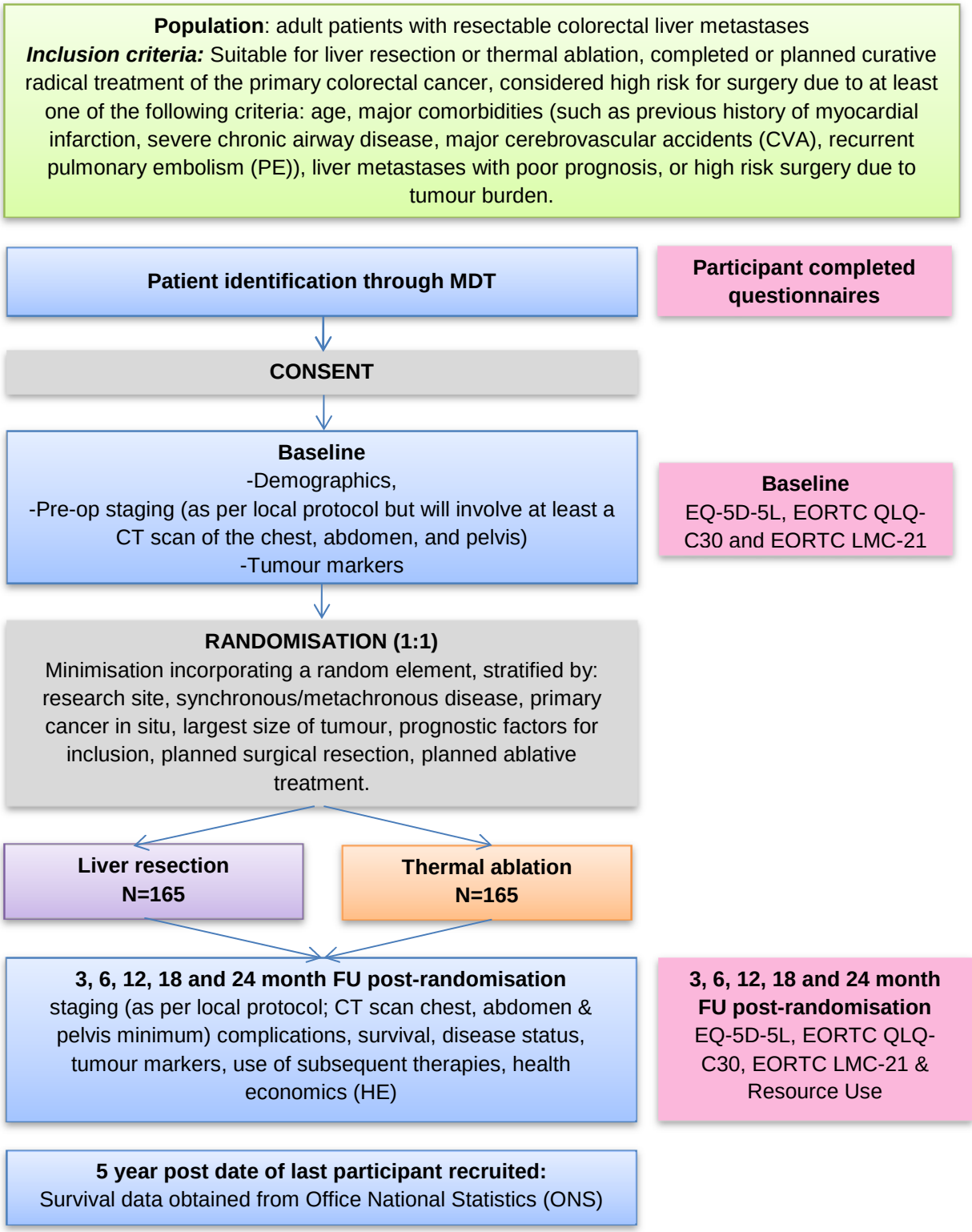
3 TRIAL SUMMARY

Trial Title	**L**iver Resection Surgery Versus Thermal **A**blation for Colorectal Li**V**er Met**A**stases
Trial Acronym	LAVA
Trial Background	Bowel cancer is the UK's second biggest cancer killer. About 30% of people with colorectal cancer develop liver metastases. Liver resection is effective in improving the life expectancy in people with colorectal liver metastases (CLM). However, only about 7% to 20% of people with colorectal liver metastases undergo liver resections because of 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 alone metastases is a main NHS goal for improving the outcome for bowel cancer patients in the UK. In light of this, specialist liver resection centres are carrying out more extensive and complex resections including elderly patients with major co-morbidity. This more extensive surgery in patients with co-morbidity is associated with an increased morbidity and mortality (high risk patients). Thermal ablation is a lower risk alternative modality for treatment of CLM and involves 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 [1] 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 to surgery in these high risk patients. Thermal ablation is currently used for patients with colorectal liver metastases not suitable for surgical resection [2] and not for patients with a possibility of curative liver resection surgery because of high local recurrence rates with thermal ablation [3]. Multiple studies have highlighted the superiority of surgery to ablation for preventing recurrence within the liver [3, 4]. A recent series from Nishiwada et al showed a 13% recurrence after surgery as opposed to 46% after thermal ablation [3]. Other newer modalities of thermal ablation include laser ablation and high intensity focused ultrasound (HIFU) [5, 6]. To determine the evidence for thermal ablation, a NIHR (National Institute for Health Research) HTA (Health Technology Assessment) funded systematic review of literature was commissioned and subsequently published in February 2014 (Loveman et al) [1]. We have reviewed this information along with subsequently published literature. There are no adequately powered trials comparing surgery with ablation therapy in patients with colorectal liver metastases. The systematic review identified one non-randomised study in which the

	survival in patients with radiofrequency ablation (RFA) was similar to liver resection surgery despite the RFA group having more comorbidities or more extensive liver metastases [7]. An exploratory cost-effectiveness analysis performed by the group on the basis of this non-randomised study showed that radiofrequency ablation 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 has also shown that patients undergoing RFA have survival comparable to surgery despite having more extensive liver metastases [4]. Similarly, an underpowered randomised controlled trial showed no difference in survival between MWA and liver surgery in resectable CLM [8]. However, in another non-randomised study published after the systematic review by Loveman et al, people who were eligible for surgery but preferred RFA had poorer survival than those undergoing surgery [9]
Trial Design	A prospective, UK and Netherlands multi-site, parallel-group, randomised trial with an internal pilot investigating the effectiveness and cost-effectiveness of liver resection surgery versus thermal ablation in high surgical risk patients eligible for liver resection. High surgical risk patients are defined as those with a high risk of post operative morbidity, mortality and reduced long term survival due to the age of the patient, their history of concurrent medical problems (co-morbidity), or the need for extensive liver resection surgery of a poor prognosis cancer.
Trial Aim	The aim of this research is to compare the effectiveness and cost-effectiveness of thermal ablation versus liver resection surgery in high surgical risk patients eligible for liver resection.
Trial Endpoints	Primary endpoint: • Disease free survival (measured from randomisation) at 2 years post-randomisation Secondary endpoints: • Overall survival at 2 and 5 years • Local and distant recurrence of disease at 2 years • Disease free survival (measured from end of intervention) at 2 years post-randomisation • Use of subsequent therapies for treatment failure • Health related quality of life (QoL) • **Complications during treatment** • Post treatment complications • Length of intensive therapy unit (ITU) and inpatient stay • Cost effectiveness

	• Explore the association between tumour markers and recurrence
Trial Population:	330 participants with resected or potentially resectable colorectal cancer with resectable liver metastases considered suitable for either liver resection or thermal ablation and who are either elderly (over 75 years), or have major co-morbidities or who have poor prognosis but resectable metastatic disease (extensive synchronous disease, two stage resection, small remnant liver volume)
Randomisation:	Minimisation incorporating a random element (1:1 allocation ratio) to undergo either liver resection surgery or thermal ablation (MWA or RFA). Randomisation to be performed by the Clinical Trials Research Unit (CTRU), Leeds.
Trial Intervention:	Liver resection will be carried out within regional centres according to individualcentre protocols. The majority of patients will have undergone resection of the primary cancer. Patients may be offered open or laparoscopic liver resection depending on site and stage of disease. In selected cases, the liver first approach may be considered. For thermal ablation, RFA or MWA will be used according to local availability and expertise. Ablation maybe performed at laparoscopic or open surgery if the percutaneous approach is contra-indicated.
Duration:	All participants are followed-up for 2 years post randomisation. Longer term survival data will be obtained from the Office of National Statistics (ONS) at 5 years post randomisation
Evaluation of outcome measures	Participants will be assessed at 3, 6, 12, 18 and 24 months post-randomisation. QoL and participant-reported outcomes (assessed using EQ5D, EORTCQLQC30, EORTC LMC21) and resource use will be measured at 3, 6, 12, 18 and 24 months post randomisation Adverse events will be documented during trial treatment and follow-up.

4 TRIAL SCHEMA



5 BACKGROUND

Bowel cancer (colorectal cancer) is the UK's second biggest cancer killer and the fourth most common cancer. Over 40,000 people are diagnosed with bowel cancer each year in the UK and about 33,000 in England alone. Just under 16,000 people die each year in the UK equating to one life every 32 minutes [10, 11]. About 30% of people with colorectal cancer develop liver metastases.

5.1 CURRENT TREATMENT OPTIONS

5.1.1 Liver resection surgery

The resection of colorectal liver metastases has provided a good long term survival for many patients who would have previously been treated with palliative therapy alone [12-15]. However, only about 7% to 20% of people with colorectal liver metastases undergo potentially curative liver resection because of the age and co-morbidities of the patient or because of the extent of cancer spread [14]. Increasing the number of patients who can undergo potentially curative therapy for liver alone metastases is a main NHS goal for improving the outcome for bowel cancer patients in the UK. In light of this, specialist liver resection centres are carrying out more extensive and complex resections including elderly patients with major co-morbidity. This more extensive surgery in patients with co-morbidity is associated with an increased morbidity and mortality (high anaesthetic risk patients, for example, patients with history of myocardial infarction, severe chronic airway disease, major cerebrovascular accidents (CVA), pulmonary embolism (PE)).

5.1.2 Thermal ablation

Thermal ablation is an alternative to surgery for the treatment of colorectal liver metastases and involves destruction of cancer by heat. Thermal ablation includes established modalities such as radiofrequency ablation (RFA) or microwave ablation (MWA). These methods are currently used for patients with colorectal liver metastases not suitable for surgical resection [2] and not for patients with a possibility of curative liver resection surgery because of highlocal recurrence rates with thermal ablation [3]. Multiple studies have highlighted the superiority of surgery to ablation for preventing recurrence within the liver [3, 4]. A recent series from Nishiwada et al showed a 13% recurrence after surgery as opposed to 46% after thermal ablation [3]. Other newer modalities of thermal ablation include laser ablation and high intensity focused ultrasound (HIFU) [5, 6]. However thermal ablation may be associated with a lower chance of cure than surgery because of the problem with local recurrence. To determine the evidence for thermal ablation, a NIHR (National Institute for Health Research) HTA (Health Technology Assessment) funded systematic review of literature was commissioned and subsequently published in February 2014 (Loveman et al) [1]. The systematic review identified one non-randomised study in which the survival in patients with radiofrequency ablation (RFA) was similar to liver resection surgery despite the RFA group having more comorbidities or more extensive liver metastases [7]. An exploratory cost-effectiveness analysis performed by the group on the basis of this non-randomised study showed that radiofrequency ablation 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 has also shown that patients undergoing RFA have survival comparable to surgery despite having more extensive liver metastases [4]. Similarly, an underpowered randomised controlled trial showed no difference in survival between MWA and liver surgery in resectable CLM [8]. However, in another non-randomised study published after the systematic review by Loveman et al, people who were eligible for surgery but preferred RFA had poorer survival than those undergoing surgery [9]

5.1.2.1 Radiofrequency ablation (RFA)

Radiofrequency ablation involves localised destruction of the tumour using heat generated by high frequency alternating current to produce coagulative necrosis of the tumour [16]. For the treatment of colorectal liver metastases, it is generally carried out as short-stay procedure under general anaesthesia, although it can also be performed under local anaesthesia in some patients [16]. Multiple sessions may be required to treat all the tumours in some patients. It can be performed percutaneously under image guidance (usually CT scan) but can also be performed by open or laparoscopic surgery [16]. Relative contraindications for RFA include lesions close to the hepatic hilum or adjacent to the hepatic duct as injury may lead to delayed stenosis of the duct and lesions abutting the bowel because of the risk of perforation [16]. Lesions near large blood vessels are often difficult to treat because of dissipation of heat by the liver circulation [16]. The dose delivered for RFA varies from one patient to another and is guided by the ablation zone diameter. The target is to heat the tissue to 60^{o} C at which coagulative necrosis occurs but to keep the electrode tip temperature below 100 ^{o} C to avoid charring and vapourisation of tissue [16]. The complications related to RFA include mortality due to massive bleeding, peritonitis resulting from intestinal perforation, or liver failure (0.2% to 0.3%). Major complications include bleeding requiring surgery or blood transfusions, liver abscesses, bile duct leaks and strictures, tumour seeding, pneumothorax, and septicaemia (2.2% to 4.1%), and minor complications such as minor bleeding, pain, skin burn, self-limiting fluid collections (4.7%) [17, 18]. Local recurrence rates are variable and range between 14% and 46% [3, 4].

5.1.2.2 Microwave ablation (MWA)

Microwave ablation involves localised destruction of the tumour using heat generated by microwave [19-21]. For the treatment of liver lesions, it is usually carried out as short-stay procedure under general anaesthesia,it can also be performed under local anaesthesia in some patients [19]. As far RFA, multiple sessions may be required in some patients to treat all the lesions. It is usually performed percutaneously under image guidance (usually ultrasound scan) [19]. It is more effective than RFA in lesions near large blood vessels [19-21]. Major technical limitations of MWA include low power, shaft heating, large diameter probes, long and relatively thin (1 to 2 cm) ablation zones, and unpredictability regarding the size and shape of the zone of ablation [19]. The complications related to MWA include mortality (0.2%), major complications such as those requiring additional unplanned hospitalisations, for example, liver abcesses or major bleeding (4.6%), and minor complications such as minor bleeding, pain, skin burn, self-limiting fluid collections (4.7% to 12%) [18, 21]. Local recurrence rates are variable and range between 14% and 38% [21].

5.1.2.3 Other ablative techniques

The vast majority of patients treated with local ablation for colorectal liver metastases undergo either RFA or MWA. However other modalities of local ablation are undergoing development including High Intensity Focussed Ultrasound (HIFU), Irreversible Electroporation Therapy (IRE)(Nanoknife therapy), Focussed radiotherapy (Cyberknife), Electrolytic therapy and Cryoblation. Cryoablation causes ice crystals resulting in vascular endothelial damage and eventually to the liver cancer[22]. The complications of cryoablation include liver failure (0.3%), bleeding (1.5%), kidney failure (1.5%), pain (31.6%), and fever (33.1%). The one year survival is around 80% while the two-year survival has variably between reported to be between 23% and 62%[22].

IRE causes cellular membrane disruption using high-voltage electrical pulses and leads to cell death without causing any damage to the underlying connective tissue scaffold[23]. This method is still being developed. The complications related to the procedure are similar to those of other percutaneous ablations but there is an added risk of cardiac arrhythmias[23].

5.1.3 Other Treatments

Other treatments such as chemotherapy are usually reserved to people with inoperable colorectal liver metastases, as adjuvant therapy to liver resection, or to downsize the unresectable colorectal liver metastases and make them resectable[24, 25].

5.2 RATIONALE FOR CURRENT TRIAL

With the development of new technologies new methods for cancer treatment are being introduced into the Healthcare market and need to be evaluated in terms of both efficacy and cost effectiveness in comparison to competing therapies. Unless this is performed, newer more cost effective therapies will not be introduced into the NHS or costly treatments which are ineffective may be adopted. This problem applies at the present time with the recent introduction of thermal ablation techniques as an alternative to surgery for the treatment of patients with CLM. If effective they should be more widely implemented in the NHS and the technology refined. If they are ineffective, support for more extensive surgery is required.

Controversies in cost-effectiveness are frequently addressed through an NIHR funded Health Technology Assessment. A recent report on clinical effectiveness and cost effectiveness of ablative therapies in the management of liver metastases suggested that a trial investigating the effectiveness and cost-effectiveness of ablation versus surgery in patients with resectable colorectal metastases is necessary [1]. The long-term results of ablation and surgery can be considered equivalent only if the difference in disease free survival between the modalities is less than 4 months due to the recovery period required following major liver surgery. However, the true difference in cancer survival between ablation and surgery in patients with CLM is not known.

'NHS England Strategic and Operational Planning 2014 to 2019' states the following 'The healthcare system is facing the challenge of significant and enduring financial pressures. People's need for services will continue to grow faster than funding, meaning that we have to

innovate and transform the way we deliver high quality services, within the resources available, to ensure that patients, and their needs, are always put first'. Clearly, it is important to maximise the health of people using the resources available.

This research will achieve this purpose of maximizing the health of people using the resources available. The results of this research can be adopted immediately in the UK because of widespread availability of expertise in both thermal ablation techniques and liver resection surgery resulting in maximisation of the health benefits using the resources available in a short period of time for high risk patients with potentially resectable colorectal liver metastases. This research may also have indirect benefit for low surgical risk patients with colorectal liver metastases on the long-term. The results of the current research will either justify the concerns of clinicians who consider that thermal ablation is inferior to surgery for the treatment of patients with CLM (in which case, no RCT comparing ablation and surgery will be conducted in low surgical risk patients as it is extremely unlikely that ablation is equivalent or better than surgery in low surgical risk patients if it offers worse results than surgery in high surgical risk patients) or it may reassure clinicians that ablation is an effective therapy (in which case, a subsequent RCT may be conducted in low surgical risk patients).

5.2.1 Choice of intervention to be investigated

The HTA review suggested that there is equipoise regarding treatment using ablation or surgery of elderly patients and those with significant comorbidities which pose significant risk from a surgical procedure and that good quality evidence of both the clinical or cost effectiveness of ablation is required [1]. From a practical aspect, the choice in the treatment of patients with potentially resectable colorectal liver metastases lies between liver resection (a modality with higher short-term mortality and complication rates and poorer quality of life during the first 3 to 6 months but with low local recurrence rates and a high potential for cure - more than 25% of patients are alive 5 years after liver resection of CLM [26]) and ablation (a less expensive modality with practically no short-term mortality, lower complication rates, earlier recovery, and higher short-term quality of life but with high local recurrence rates and the crucial uncertainty of whether it could offer similar long-term cancer related outcomes as liver resection [27]).

5.2.1.1 Potential advantages/concerns of thermal ablation over surgery

Current evidence suggests that thermal ablation has lower complication rates and better health-related quality of life than surgery [1]. Thermal ablation is also less expensive than liver resection [1], which will result in cost savings to NHS. Ablation therapy has the potential to decrease the pain after treatment and time taken for recovery from cancer therapy which will decrease the number of work days lost by the patient and their carer resulting in a financial impact on patients, their carers, and their employers.

The major concern about thermal ablation is the high incidence of local recurrence. As a result it would be anticipated that it will not offer similar cancer related outcomes as liver resection surgery. However in patients who are high risk but would currently be considered for liver resection [27] the short and long term outcomes after surgery are likely to be poorer than the normal surgical cohort and hence thermal ablation for this group may produce comparable results.

5.2.1.2 Comparison of thermal ablation to surgery

Liver resection for colorectal liver metastases is a major surgical procedure and carries a post-operative mortality of approximately 3% to 4% and a complication rate of about 40% [26]. Because of the effects of major surgery and the associated pain, the patients take about 2 to 3 months to recover from surgery and the quality of life is only 0.65 on a scale of 0 to 1 (1 indicating perfect health) even after 6 months after liver resection [1]. As the patient group identified for this trial are those considered high risk in terms of age, co-morbidity and the extent of liver resection required, the mortality, morbidity, length of hospital stay are likely to be considerably higher than the average and the health related QoL and recovery period significantly greater.

In contrast, the ablative methods have fewer complications (6%) [7] and the quality of life is 0.74 (on a scale of 0 to 1) by 3 months [1]. An informal discussion with patient representatives from Bowel Cancer UK suggested they were willing to trade-off between 3 to 6 months (average 4 months) of their long-term survival in return for a less invasive procedure with significantly lower complication rates compared to surgery. So, on average, the long-term results of ablation and surgery can be considered equivalent as long as the difference in long-term survival between the modalities is less than 4 months. Clearly, if ablation results in a better survival, ablation is the better option since it is less invasive and results in better quality of life in the short-term.

5.2.1.1 Comparison of methods of thermal ablation

Non-randomised studies comparing microwave ablation (MWA) with radiofrequency ablation (RFA) suggested that MWA is better than RFA in terms of technical feasibility and lower disease recurrence in patients with unresectable CLM [1]. Of the newer forms of ablative methods such as high intensity focussed ultrasound (HIFU), cyberknife, cryotherapy, there are no publications comparing these newer ablation methods with either RFA or MWA. In reality, different surgeons and radiologists have their own preferences of method of ablation because of this uncertainty.

5.2.2 Choice of patient group to be investigated

There has been no adequately powered randomized controlled trial comparing ablation versus surgery in patients with colorectal liver metastases. Retrospective cohort studies highlight the high local recurrence rate associated with thermal ablation in comparison to liver resection surgery but a much lower procedure related morbidity and mortality [3, 4]. The options include performing a randomized controlled trial for low risk patients (young patients without comorbidities with limited extent of cancer spread) with CLM, high risk patients with CLM, or all patients with CLM who are suitable for undergoing liver resection. There is good long-term data on efficacy of surgical resection. Surgical resection provides low rates of local recurrence and disease free survival proportions of about 28% [26]. However, there is a high rate of local recurrence following thermal ablation and a lack of long-term data on the efficacy of ablation in patients with CLM. In light of the known rates of local recurrence and the lack of long-term data on cancer outcomes, the majority of clinicians feel that it is unethical to randomise low-risk patients to ablation or surgery despite the short-term benefits of lower complication rates, less pain and lower costs in patients undergoing ablation.

While some non-randomised studies did not justify these concerns demonstrating equivalent survival between RFA and liver resection despite patients undergoing RFA having more comorbidities or more extensive disease [4, 7], another non-randomised study supported these ethical concerns and demonstrated that RFA had poorer 5- year survival compared to surgery, the only difference between the patient groups being their preference for RFA or surgery [9].

However, with high-risk patients, there is significant uncertainty as to the benefits of surgery and majority of clinicians feel that there is equipoise between these modalities for this patient group. These patients have 1.5 times to 2 times lower survival than low surgical risk patients [28-30]. In this research, we will compare the effectiveness and cost-effectiveness of ablation versus surgery in this high risk group of patients. If this research shows equivalent results of thermal ablation and surgery in this group, this will provide background data for a subsequent clinical trial on other patient groups, such as low-risk patients.

6 AIMS AND OBJECTIVES

6.1 AIM

The aim of this research is to compare the effectiveness and cost-effectiveness of thermal ablation versus liver resection surgery in high surgical risk patients eligible for liver resection.

6.2 OBJECTIVES

Pilot study objectives:

1. To assess the feasibility of recruitment
2. To assess the quality of ablations and if required revise the ablation protocol for the main trial
3. To assess the quality of liver resection surgery in terms of completeness of resection, morbidity and mortality and determine acceptable surgical standards for the main trial
4. To centrally review the reporting of CT scan findings relating to ablation outcomes and recurrence (in both arms) to ensure quality reporting.

Main trial objectives:

1. To compare the following outcomes between ablation and surgery.
    a. Primary outcome.
        i. Disease free survival (measured from randomisation) at 2 years post-randomisation

    b. Secondary outcomes
        i. Overall survival at 2 and 5 years post-randomisation.
        ii. Local and distant recurrence of disease at 2 years post-randomisation.
        iii. Disease free survival (DFS) (measured from end of intervention)at 2 years post-randomisation
        iv. Use of subsequent therapies for treatment failure over 2 years post-randomisation.

v. Health related quality of life (EQ-5D, EORTC QLQ-C30, EORTC LMC21) [31-33] at baseline, and 3, 6, 12, 18, and 24 months post-randomisation.

vi. Complications during treatment
vii. Post treatment complications.
viii. Length of intensive therapy unit (ITU) and inpatient stay.
ix. Resource use collected retrospectively at 3, 6, 12, 18, and 24 months post-randomisation

2. Assess the cost and cost-effectiveness of ablation versus surgery (based on the Health related quality of life and Resource use data collected during the trial).
3. Assess the effectiveness and cost effectiveness of RFA and MWA by subgroup analysis.
4. Explore the association between tumour markers and recurrence (as defined in section 15.1)

7 DESIGN

A prospective, international (UK and the Netherlands), multi-site, open, pragmatic, parallel-group, randomised controlled trial design with internal pilot to investigate the effectiveness and cost-effectiveness of thermal ablation (RFA or MWA) compared to liver resection for the treatment of patients with resectable colorectal liver metastases who would be considered high risk for surgery and with a low chance of cure.

330 participants will be randomised on an equal basis to either liver resection surgery or thermal ablation. The follow-up period finishes 2 years after the last participant is randomised. Long term survival data will be obtained from the Office of National Statistics (ONS) at 5 years after the last participant is randomised.

The trial will not be blinded to participants, medical staff, or clinical trial staff, given the difference between the two interventions being compared.

7.1 Internal pilot

An internal pilot will run within the first year of recruitment into the trial. The feasibility of recruitment will be explored (see section 24 for details of the qualitative sub-study). The standard of ablation and surgery, according to reported treatment outcomes – i.e. completeness of ablation/resection and post-treatment morbidity and mortality – will be monitored and treatment protocol/guidance will be amended as required based on findings. All CT scans performed to assess the outcome of the ablation intervention (i.e. scans typically carried out around 4-6 weeks after the last ablative session of treatment) for participants in the ablation arm will undergo central review during the pilot stage (see section 11.6). Data quality for key fields such as the stratification factors will also be assessed during the pilot phase. Findings from the pilot will inform whether any changes are required to the trial design and if so, this will be done through an amendment to the protocol after discussions with the TSC and DMEC

8 ELIGIBILITY

8.1 RESEARCH SITE ELIGIBILITY

The trial will open in at least 20 research sites throughout the UK and the Netherlands. Each site must fulfil a set of pre-specified criteria and complete a registration form which verifies that the research site is willing and able to comply with the trial requirements. This will be signed by the proposed local Principal Investigator (PI) on behalf of all staff who will be affiliated with the trial. Research sites will be required to obtain local management approval, return all required essential documentation to CTRU and undertake a site initiation with the CTRU prior to the start of recruitment into the trial.

Participation of research sites will be dependent upon the following criteria:

1. Site must be a tertiary liver, pancreatic and gallbladder (HPB) centre
2. Site must have experience in the provision of liver resection surgery and thermal ablation for CLM
3. Site must have a shared specialised MDT with representatives from surgery and radiology

8.2 SURGEON / RADIOLOGIST ELIGIBILITY

All surgeons and radiologists in the trial will have carried out a minimum of the following relevant prior procedures:

a. To perform liver resections within the trial: prior experience of performing liver resection procedures for a minimum of 20 patients with liver cancer

b. To perform thermal ablation within the trial: prior experience of performing ablative procedures for a minimum of 20 patients with liver cancer

8.3 PATIENT ELIGIBILITY

Eligibility waivers to inclusion or exclusion criteria are not permitted.

8.3.1 Inclusion criteria

1. Aged ≥ 18 years
2. Able to provide written informed consent
3. MDT diagnosis of colorectal liver metastases considered to be resectable or ablatable with curative intent

4. Resected colorectal primary or plan[1] for primary resection with curative intent
5. Meets ***one or more*** of the following criteria:
    i) Considered high risk for surgery due to age e.g. age greater than 75 years
    ii) Major co-morbidities as judged by the treating clinician. Examples include history of myocardial infarction, severe chronic airway disease, major cerebrovascular accidents (CVA), pulmonary embolism (PE)
    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 extra-hepatic disease[2], downstaged with chemotherapy, poor response after chemotherapy but still resectable or ablatable.
6. Suitable candidate for either liver resection surgery or thermal ablation as judged by the MDT [3]
7. Able and willing to comply with the terms of the protocol including QoL questionnaires

8.3.2 Exclusion criteria

1. Incurable extra-hepatic metastases
2. Not a suitable candidate for liver resection surgery
3. Not a suitable candidate for thermal ablation
4. Concurrent malignant disease (except basal cell carcinoma)
5. Patients who have undergone previous surgery or ablation for colorectal liver metastases
6. Planned simultaneous resection of primary and liver metastases
7. Pregnancy[4]

8.3.3 Concurrent clinical trials

Participants will not be eligible for entry into other clinical trials of surgical/ablative technique. However patients will be suitable for inclusion in LAVA if they have already participated in a previous non-surgical/ablative trial. Please contact the Clinical Trials Research Unit (CTRU, University of Leeds) for further clarification.

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[1] Where liver first treatment is planned. If there is a plan to resect the colorectal primary prior to treatment of the liver metastases, the participant should be randomised following resection of the colorectal primary.

[2] Where liver first treatment is planned. If there is a plan to treat the curable extra-hepatic disease prior to treatment of the liver metastases, the participant should be randomised following treatment of the extra-hepatic disease.

[3] Suitability assessment includes general fitness.

[4] It is the local site's responsibility to ensure this is assessed in women of child-bearing potential according to local standard of care

9 RECRUITMENT PROCESS

9.1 RECRUITMENT SETTING

Participants will be recruited from tertiary HPB centres in the UK and in the Netherlands. A total of 330 participants (165 in each arm) will be recruited into the trial over a 48-month period. Research site set-up, recruitment of participants and pilot study findings will be reviewed approximately 12 months from opening.

9.2 ELIGIBILITY SCREENING

Participating research sites will be required to complete a log of all patients screened for eligibility who are not randomised either because they are ineligible or because they decline participation. Anonymised information will be collected including:

- Age
- Gender
- Ethnicity
- Date screened
- Reason not eligible for trial participation, or
- Eligible but declined and reason for this, or
- Other reason for non-randomisation
- If eligible and not randomised, treatment planned and/or received for liver metastases will also be collected

This information will be requested from research sites on a regular basis (at least 3 monthly) by the CTRU.

9.3 INFORMED CONSENT

Patients will be approached for possible recruitment following MDT diagnosis and decision to treat. Where applicable, if there is a plan to resect a colorectal primary or treat curable extra-hepatic disease prior to treatment of the liver metastases, patients should be approached and randomised following further MDT review after resection of the colorectal primary or treatment of the extra-hepatic disease.

Suitability for inclusion into the trial will be assessed according to the eligibility criteria and patients will be provided with verbal and written details. A verbal explanation of the trial along with the approved PIS/ ICF will be provided by a medically qualified member of the healthcare

team for the patient to consider. The PIS will provide detailed information about the rationale, design and personal implications of the trial.

Following information provision, patients must be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they would be willing to take part in the trial. Patients will be given as much time as possible to consider their participation in the trial; ideally they will be allowed 24 hours as a minimum. The right of the patient to refuse consent without giving reasons will be respected.

Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent for their participation in the trial, including explicit consent for the transfer of a copy of their signed consent form to the CTRU.

Informed consent may only be obtained by the PI or an appropriate healthcare professional. The healthcare professional must have knowledge of the trial interventions and have received training in the principles of GCP and the Declaration of Helsinki 1996. He/she must be fully trained in the trial according to the ethically approved protocol and be authorised and approved by the PI to take informed consent as documented in the trial APL. The PI retains overall responsibility for the informed consent of participants at their research site

The patient consent form with all original signatures must be retained in the ISF. A copy of the signed consent form must be given to the participant, and a record of the consent process, detailing the date of consent and witnesses, must also be kept in the participant's medical notes (this may include a copy of the consent form as per local practice). A copy of the signed consent form must also be transferred to the CTRU.

Participants will remain free to withdraw from the trial at any time by revoking consent without giving reasons and without prejudicing any further treatment.

There is also a planned qualitative sub-study which will take place during the pilot phase of the trial which will involve recording of recruitment encounters and patient being interviewed (see Section 24 for full details). Patients who decline to participate in the trial will still be eligible for this sub-study.

9.3.1 Loss of capacity following informed consent

Loss of mental capacity of a participant after giving informed consent for the trial is expected to be a rare occurrence. Should this eventuality occur, this should reported to CTRU via a withdrawal form with no further trial procedures or data collection occurring from this point. Any data collected up to the point of withdrawal will be kept on record and used in the trial analysis.

9.4 RANDOMISATION

Informed written consent for entry into the trial must be obtained prior to randomisation.

9.4.1 Timing of randomisation

Randomisation should take place as soon as possible after consent is obtained and after participants have completed their baseline participant-completed questionnaire (see section 11.5). Baseline participant-completed questionnaires must be collected immediately prior to randomisation to avoid bias in questionnaires occurring due to patient knowledge of randomisation allocation. The interval between randomisation and surgery/ablation must be kept to a minimum, and wherever possible should not exceed 30 days.

9.4.2 Randomisation process

Following confirmation of written informed consent and eligibility, the participant-completed questionnaires should (wherever possible) be completed prior to randomisation, however where this is not possible, these must be completed prior to the participant being made aware of their randomised treatment (surgical resection or ablation). Participants will be randomised into the trial by an authorised member of staff at the research site. Randomisation will be performed centrally using the CTRU 24 hour randomisation service, either via the telephone or the CTRU website. Authorisation codes and PINs, provided by the CTRU, will be required to access the 24-hour randomisation telephone service, whilst authorised personnel will be able to use their email address and PIN to access the web based randomisation service.

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Please complete the Randomisation Form prior to accessing the 24-hour registration/randomisation service. The following information will be required at randomisation:

- Participant details, including initials and date of birth
- Name and code of the research site
- Name of the person making the randomisation
- Confirmation of eligibility
- Confirmation of written informed consent
- Stratification factors (see section 9.4.3)

Once randomisation is complete, the randomisation service will allocate participants a unique 5 digit trial number and inform of the randomised treatment for that participant (surgical resection or ablation).

24-hr direct line for randomisation: 0113 343 2290

Web page for randomisation:
https://lictr.leeds.ac.uk/webrand/

9.4.3 Treatment allocation

Participants will be randomised on a 1:1 basis to receive either surgical resection or thermal ablation and will be allocated a unique trial number. A computer-generated minimisation programme that incorporates a random element will be used to ensure treatment groups are well-balanced for the following participant characteristics, details of which will be required for randomisation:

- Research site
- Synchronous/metachronous disease
- Primary cancer in situ (Yes/No)
- High risk for surgery due to age (Yes/No)
- Major co-morbidity (Yes/No)
- Poor prognosis or high risk surgery due to tumour burden (Yes/No)
- Largest lesion size ≤ 5 cm (Yes/No)[29]
- Planned surgical resection
    - Open
    - Laparoscopic
- Planned ablative treatment
    - Radiofrequency (RFA)
    - Microwave (MWA)

10 INTERVENTION DETAILS

10.1 SCHEDULE OF CLINICAL ASSESSMENTS/DATA COLLECTION POINTS

The timing of clinical assessments and data collections points are summarised in Table 1. All participants will be followed up via clinic visits as per protocol until 24 months post-randomisation

Table 1: Schedule of Events

	Events	Baseline	Treatment of the index disease[1] (surgical resection or thermal ablation)	3, 6, 12, 18, 24 months Post-randomisation Assessment
Clinical Assessments	Clinical examination[2]	√		√
	Imaging investigation (CT scan chest abdo, pelvis min)	√[3]		√[4]
	Tumour markers – (carcino-embryonic antigen CEA, CA19-9))	√		√[4]
	Treatment details		√	
	Complications[5]		√	√
	Trial Consent	√		
Data collection timepoints	Eligibility CRF	√		
	Baseline CRF	√		
	Treatment CRF		√[6]	
	Post treatment CRF		√[6]	
	Follow-up CRF			√
Participant completed questionnaires	EQ-5D	√		√
	EORTC LMC21	√		√
	EORTC QLQ-C30	√		√
	Resource Use	√		√

[1] See Section 10.3.1 for the definition of the index disease.

[2] At baseline this includes data collection on demographics, co-morbidity, results of investigations. These will vary between research sites but will include staging tests (CT scan chest abdo pelvis minimum) assessment of fitness (e.g. cardiac echo, stress echo, coronary angio, pulmonary function, treadmill test, CPEX)

[3] Must be within 6 weeks prior to start of the trial intervention

[4]These investigations only need to be performed following completion of successful treatment for the index disease and until disease recurrence.

[5]For information on reporting treatment-related complications, please refer to section 12

[6]This is a repeating form. A separate treatment form/post-treatment form should be filled in for each operation/ablative session performed as part of the trial intervention (defined in section 10.3)

10.2 PRE-TREATMENT INVESTIGATIONS AND PREPARATION

Pre-treatment investigations and preparation will be as per institutional protocol, butmust include stagingCT scan of chest, abdomen and pelvis as minimum along withtumour markers.

10.2.1 Staging

A baseline staging investigation (CT scan chest, abdomen and pelvis minimum) must be performed prior to (but not more than 6 weeks before) the start of the trial intervention.

10.2.2 Tumour markers

Tumour markers i.e. CEA as minimum (but may include Ca19-9 as per local policy) should be performed prior to (but not more than6 weeks before) the start of treatment.

10.3 INTERVENTION DETAILS

10.3.1 Definition of index disease

Index disease is defined as the disease distribution of colorectal liver metastases at the time of the most recent assessment (specialist multidisciplinary team sMDT review) prior to the treatment commencing.

10.3.2 Surgical resection

For participants in the surgical resection arm, the intervention is defined as the operation or collection of operations conducted as treatment for the disease. distribution of colorectal liver metastases at the time of the most recent assessment (specialist multidisciplinary team sMDT review) of prior to the treatment commencing (specialist multidisciplinary team sMDT review), which will be considered as the index disease.

Surgical liver resection will be performed in accordance with each site's usual practice. Patients may be offered open or laparoscopic liver resection depending on site and stage of disease. Procedures for patients with extensive metastatic disease can include two stage liver resection, portal venous embolization, or the ALPPS procedure (Associated Liver Partition and Portal vein ligation for Staged hepatectomy).

Minimum surgical standards to be achieved during the trial will be discussed at the pre-trial standardisation meeting and will be detailed in the LAVA Site Standard Operating Procedure (SSOP)

10.3.2.1 End of trial treatment definition

End of trial treatment in the surgical resection arm is defined as the end of the final operation in the collection of operations conducted as treatment of the index disease.

10.3.3 Thermal ablation

For patients in the thermal ablation arm, the intervention is defined as the collection of ablation sessions conducted as treatment for the disease distribution of colorectal liver metastases at the time of the most recent assessment (specialist multidisciplinary team sMDT review) prior to the treatment commencing ,which will be considered as the index disease.

For participants in the thermal ablation arm, either radiofrequency ablation (RFA) or microwave ablation (MWA) will be carried out according to the local availability of equipment and expertise. Ablation may be performed at laparoscopic or open surgery if the percutaneous approach is contra-indicated.

Minimum ablation standards to be achieved during the trial will be discussed at the pre-trial standardisation meeting and will be detailed in the LAVA Site Standard Operating Procedure (SSOP)

10.3.3.1 End of trial treatment definition

End of trial treatment in the ablation arm is defined as the end of the final ablation session in the collection of ablation sessions conducted as treatment of the index disease.

10.4 POST-TREATMENT CARE

Post-operative care will be as per standard practice, but participants must be reviewed in clinic at the following timepoints:

- **3, 6, 12, 18 and 24 months post-randomisation (+/- 4 weeks)**
    - The following investigations should be performed following completion of successful treatment of the index disease until disease recurrence:
        - Follow-up imaging investigation (CT scan chest, abdomen & pelvis minimum)
        - Tumour markers

Any further visits will be according to local standard clinical practice, but will be captured on the follow-up Case Report Form (CRFs).

10.5 FURTHER TREATMENTS

Further chemotherapy will be offered to patients as per current practice. Treatment of recurrent disease will depend of the site and extent of disease and will be decided following review by the multi-disciplinary group at the specialist liver MDT and following discussion of

the treatment options with patients and their family. Treatment options will not be influenced by the randomisation within the trial.

10.6 WITHDRAWAL OF TREATMENT

In line with usual clinical care, cessation or alteration of treatment at any time will be at the discretion of the attending clinician or the participant themselves.

In the event that a participant withdraws prior to randomisation, no further data is required to be submitted. In the event that a participant withdraws after randomisation but prior to index disease treatment, collection of follow-up data will still be required. For participants withdrawing from the trial after index disease treatment, they will still attend follow-up visits unless unwilling to do so and safety data and follow-up data will continue to be collected.

If a participant explicitly states they do not wish to contribute further data to the trial or to complete any further participant questionnaires, the CTRU must be informed in writing.

The PI or delegate must make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the Withdrawal CRF in order that the correct processes are followed by the CTRU and research site following the withdrawal of consent.

11 DATA COLLECTION

Participating research sites will be expected to maintain a file of essential trial documentation (ISF), which will be provided by the CTRU, and keep copies of all completed CRFs for the trial. The CRFs and participant-completed questionnaires will contain the participant's unique trial number, date of birth, and initials. Clinical data will be collected at baseline, treatment, and at 3, 6, 12, 18 and 24 months post-randomisation; participant-completed data will be collected at baseline, and at 3, 6, 12, 18 and 24-months post-randomisation.

11.1 SUBMISSION OF TRIAL DATA

Participating research sites will record trial participant data on trial-specific paper CRFs and submit them to the CTRU. Missing and discrepant data will be flagged and additional data validations raised as appropriate from the CTRU data management team.

11.2 PRE-TREATMENT DATA COLLECTION

Participants must be screened, assessed for eligibility and have provided written informed consent before they can then be randomised (Section 9.4).

Data collected on the pre-treatment CRFs (Eligibility Checklist, Baseline and Randomisation Forms) will include (but will not be limited to):

- Personal details and demographics including height, weight, gender, and American Society of Anesthesiologists (ASA) grade

- Results of pre-treatment investigations: These will vary between research sites but will involve a minimum of tumour markers and results of staging. Other investigations may include cardiac echo, stress echo, coronary angio, pulmonary function, treadmill test, CPEX)
- Known co-morbidities
- Other information required to confirm eligibility

Following written informed consent and wherever possible prior to randomisation (where this is not possible this must be prior to the participant being made aware of their randomised treatment) participants will also be asked to complete the baseline participant-completed questionnaires:

- EQ-5D-5L
- EORTC-QLQC30
- EORTC LMC21
- Health and Social Care Resource Use

11.3 INTERVENTION DATA COLLECTION

11.3.1 Treatment Details Data Collection

A separate treatment CRF will be completed for each operation/ablation session performed as part of the trial intervention (defined in section 10.3). This will collate data relating to the surgical resection/thermal ablation including (but not limited to):

- Performed treatment (type of resection, type of ablation)
- Duration of treatment
- Any intra-treatment complications[5]

11.3.2 Post Treatment Data Collection

A separate post treatment CRF will be completed 4-6 weeks after each operation/ablation performed as part of the trial intervention (defined in section 10.3). This will collate data including (but not limited to):

- Trial intervention outcome i.e. confirmation of (in)completeness of removal/eradication of the index disease
- Duration of post- treatment hospital stay
-

[5] Some complications will require expedited reporting to CTRU, please see Section 12 for more details

11.4 FOLLOW-UP DATA COLLECTION

11.4.1 Data Collection for clinical assessments

At 3, 6, 12, 18 and 24 months from randomisation (+/- 4 weeks), a clinical assessment must be carried out for all participants.

Data collected during follow up will include (but will not be limited to):

- Post-treatment complications and severity[6]
- Details of any further referrals or interventions required and reason
- Medications
- Results of follow up imaging investigation scans
- Disease status
- Tumour marker results
- Additional interventions including any chemotherapy given

11.5 PARTICIPANT-COMPLETED QUESTIONNAIRES

Participant- completed questionnaires measuring quality of life (EQ-5D, EORTC QLQ-C30, EORTC LMC21) will be completed in clinic at baseline and posted out to participants for completion at 3, 6, 12, 18 and 24 months post-randomisation (see section 13).

Wherever possible, these patient-completed questionnaires must be completed at 3, 6, 12, 18and 24 months post-randomisation, +/- 2 weeks.

Patient-completed questionnaires measuring health and social care resource use will be posted out to participants for completion at 3, 6, 12, 18 and 24 months post-randomisation. Participants will be asked to record use of health and social care services, including medications, since the previous questionnaire was completed (or since hospital discharge from index treatment in the case of the questionnaire at 3 months post-randomisation).

[6] Some complications will require expedited reporting to CTRU, please see Section 12 for more details

11.6 CT SCAN CENTRAL REVIEW

11.6.1 ABLATION ARM CT SCAN CENTRAL REVIEW

All CT scans performed to assess the outcome of the ablation intervention (e.g. baseline scans and scans typically carried out around 4-6 weeks after the last ablative session of treatment) will be centrally reviewed for participants in the thermal ablation arm during the pilot phase. The central review will facilitate quality assurance of local interpretation of the CT scan findings e.g. the completeness/"success" of the treatment, the need for further sessions etc.

To ensure quality assurance following the pilot study, we will undertake a review of thermal ablation by the trial interventional radiologists in a further 20% of the patients chosen at random. The outcome of this review process will be presented at the meetings of the Trial Management Group (TMG) and the Independent Trial Steering Committee (TSC) who will be responsible for feed back to the radiology leads at individual research sites.

It is the responsibility of each research site to remove all personal identifiable data from CT scans prior to sending to the CTRU. CT scans should be in the standard DICOM format and labelled with the trial number, date of birth and initials

11.6.2 FOLLOW UP CT SCAN CENTRAL REVIEW

To ensure quality assurance of the reporting of recurrence, which feeds into the primary endpoint, a subset of CT scans performed during the follow up period (at around 3, 6, 12, 18 and 24 months post-randomisation) will be chosen at random for central review. The selection process will be stratified by centre and outcome (recurrence/no recurrence) so that the accuracy of reporting of both "recurrence" and "no recurrence" can be assessed across all participating centres.

11.7 PREGNANCY

Any suspected or confirmed pregnancies between the date of randomisation to the end of index disease treatment must be reported to the CTRU **within 7 days** of the research site becoming aware. All further protocolised treatment must be stopped immediately if a pregnancy occurs or is suspected during this time; it is the responsibility of the treating surgeon/radiologist to decide what course of action should be taken in relation to ensuring the participant's ongoing treatment outside of the trial protocol.

The CTRU will inform the Sponsor of all reported pregnancies.

11.8 DEATH

All deaths must be recorded on the Notification of Death CRF. Data collected will include (but will not be limited to):

- Date of death
- Cause of death

Deaths occurring in the trial population from randomisation to 24 months post -randomisation must be reported on the Notification of Death CRF. If a participant dies within 6 months of the end of trial treatment, a completed Notification of Death CRF must be faxed **within 7 days** of site becoming aware of the event. The original form must then be posted to the CTRU and a copy retained at the research site. If a participant dies more than 6 months after the end of trial treatment then a completed Notification of Death CRF will be collected with follow-up data and returned with the 12, 18 or 24-month follow-up CRFs to the CTRU (see section 11.4).

11.9 DEFINITION OF END OF TRIAL

The end of the trial is defined as the date of the last participant's last data item.

12 SAFETY REPORTING

For the purpose of the trial, which involves surgical and ablative interventions, the safety reporting terms adverse events and serious adverse events have been translated into complications.

12.1 GENERAL DEFINITIONS

A **complication** is defined as an untoward medical event in a participant, which has a causal relationship to the trial. The trial includes the trial intervention as defined in section 10.3 and any further treatment related to the trial intervention (such as treatment of complications caused by the trial intervention and any trial-specific interventions e.g. the consent process and completion of questionnaires).

An untoward medical event can include:

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing condition
- any clinically relevant deterioration in any clinical tests

A **serious complication (SC)** is defined as a complication which:

- results in death
- is life-threatening[7]
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity

[7] Life-threatening refers to an event in which the participant was at risk of death at the time of the event, NOT an event which hypothetically may have caused death had it been more severe.

- consists of a congenital anomaly or birth defect, or
- is otherwise considered medically significant by the investigator

An **Unexpected Serious Complication (USC)** is a **serious** complication which is **related** and **unexpected**will require expedited reporting (see section 12.3.2) to enable reporting to the main Research Ethics Committee (REC) and Sponsor.

The Health Research Authority (HRA) defines the terms **related** and **unexpected** as:

- **Related**: that is, it resulted from administration of any research procedures. All complications by definition are related to the trial procedures. (Untoward medical events which are unrelated to the trial procedures are not being collected in this trial.)
- **Unexpected**: that is, the type of event that in the opinion of the investigator is not considered expected. Examples of expected complications are provided in section 12.2; note this is not an exhaustive list.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see section 12.4 for Responsibilities). These characteristics/ consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

12.2 EXPECTED COMPLICATIONS

12.2.1 Operative Expected Complications

- Bleeding requiring blood transfusion or re-operation
- Liver failure
- Liver damage
- Liver abscesses
- Septicaemia and its consequences (multiorgan failure)
- Surgical site infections
- Fluid collections requiring reoperation or drainage
- Self-limiting fluid collections
- Pneumonia
- Atelectasis
- Myocardial infarction
- Heart failure

- Stroke
- Deep vein thrombosis
- Pulmonary embolism
- Respiratory failure
- Pain
- Dyspnoa
- Confusion
- Nausea
- Vomiting
- Immobility
- Anorexia

12.2.2 Ablation Expected Complications

- Bleeding requiring blood transfusion or operation
- Peritonitis resulting from intestinal perforation
- Liver failure
- Liver damage
- Liver abscesses
- Septicaemia and its consequences (multi-organ failure)
- Fluid collections requiring operation or drainage
- Self-limiting fluid collections
- Pneumothorax
- Pain
- Skin burn
- Dyspnoea
- Confusion
- Nausea
- Vomiting
- Immobility

12.3 REPORTING OF COMPLICATIONS

Information on all complications will be collected for this trial whether volunteered by the participant, discovered by investigator questioning or detected through physical examination or other investigation.

12.3.1 Classification of complications

All complications should be graded using the Clavien-Dindo Classification scale[34] where appropriate. Note that the Clavien-Dindo classification scale was developed for grading post-operative complications for patients who underwent surgery, but is thought to be equally applicable to patients who have undergone ablation – see Appendix 1 for details.

12.3.2 Serious Complication (SCs) and Unexpected Serious Complications (USCs) occurring within 30 days of treatment – Expedited reporting

All Serious Complications (SCs) and Unexpected Serious Complications (USCs) (see section 10.1) occurring within 30 days of any trial treatment are subject to expedited reporting requirements and must therefore be notified to the CTRU **within 24 hours** of the clinical research staff becoming aware of the event. Notifications must be sent to CTRU by fax using the SC / USC CRF. Once all resulting queries have been resolved, the CTRU will request the original form is posted to the CTRU and a copy retained at site.

24 hr fax for reporting SC & USCs: 0113 343 0686

For each SC and USC, the following data will be collected:

- Start and end dates of event, if resolved
- Full details of complication in medical terms with a diagnosis (if possible)
- Action/intervention
- Outcome
- An identifiable and authorised reporting source (i.e. the signature of the investigator or other medic authorised by the investigator at the reporting research site)

Any follow-up information on SCs and USCs must be faxed or emailed to the CTRU as soon as it is available. Events will be followed up until resolution or a final outcome has been reached. All USCs will be reviewed by the Chief Investigator (CI) and will be subject to expedited reporting to the Sponsor and the REC by the CTRU on behalf of the CI in

accordance with current HRA guidance, CTRU Standard Operating Procedures (SOPs), and Sponsor requirements.

SCs and USCs with an onset date greater than 30 days post-index treatment are not subject to expedited reporting, but must be reported with all other types of complication (i.e. non-serious expected and unexpected complications) via a post-operative complication form submitted with the 4-6 weeks post treatment, or 3, 6, 12, 18 & 24-months Post-randomisation Follow Up Assessment CRFs, as appropriate (see section 12.3.3).

12.3.3 All other complications – Non-expedited reporting

Information about the incidence and severity of all other complications (this includes all non-serious expected and unexpected complications) which occur from the date of initial treatment until 24 months post-randomisation will be collected for all participants on the treatment CRF, 4-6 weeks post treatment, or 3, 6, 12, 18 & 24-months Post-randomisation Follow Up Assessment CRFs, as appropriate. This also applies to any SCs or USCs with an onset date greater than 30 days post-surgery.

These events will **not** be subject to expedited reporting requirements.

12.3.4 Untoward medical events unrelated to the trial – Not reportable

It is anticipated that there will be minimal additional risks associated with the interventions in this trial. Participants treated may have co-morbidities and in recognition of this, untoward medical events will only be reported if they are classified as related to trial procedures (including the surgical/ablative intervention and related procedures or trial-specific procedures such as consent and questionnaire completion).

12.4 RESPONSIBILITIES FOR SAFETY REPORTING

Principal Investigator (PI) (i.e. lead trial clinician at each recruiting research site or appropriate clinical individual identified in the APL)

- Checking for complications during admission and follow-up, including judgment in assigning:
    - Causality, i.e. whether an untoward medical event is related (i.e. a complication which therefore needs to be reported) or unrelated (i.e. not a complication and therefore does not need to be reported)
    - Seriousness
    - Expectedness
- To ensure all SCs and USCs up to 30 days post-treatment are recorded and initially reported to the CTRU within 24 hours of the research site team becoming aware and to provide further follow-up information as soon as available.
- To report SCs and USCs to the CTRU in-line with the protocol.

- To report USCs to local committees in line with local arrangements.

Chief Investigator (CI) (or nominated individual in CI's absence)

- Assign relatedness and expected nature of reported complications/untoward medical events where it has not been possible to obtain local assessment.
- Undertake review of SCs and USCs (see section 12.3.2).
    - In the event of disagreement between local assessment and the CI, local assessment may be upgraded or downgraded by the CI prior to reporting to the REC.

Clinical Trials Research Unit (CTRU)

- Expedited reporting of USCs occurring within 30 days post-treatment to the REC and Sponsor within required timelines.
- Preparing annual safety reports to the REC and periodic safety reports to the Trial Steering Committee (TSC) and Data Monitoring & Ethics Committee (DMEC) as appropriate.
- Notifying Investigators of SCs and USCs which compromise participant safety.

Trial Steering Committee (TSC)

- Periodic review of safety data in accordance with the TSC Terms of Reference, and liaising with the DMEC regarding safety issues.

Data Monitoring & Ethics Committee (DMEC)

- In accordance with the DMEC Terms of Reference, periodic review of unblinded overall safety data to determine patterns and trends of events and to identify any safety issues which would not be apparent on an individual case basis.

12.5 ONWARD REPORTING

Safety issues will be reported to the REC as part of the annual progress report.

An annual summary of complications will be reported to the TSC and Sponsor.

Expedited reporting of events (as detailed in section 12.3.2) to the REC. and Sponsor will be subject to current HRA guidance, CTRU SOPs and Sponsor requirements.

13 PARTICIPANT QUESTIONNAIRES

Participants will complete a number of health related quality of life questionnaires

- **EQ-5D-5L:** a validated questionnaire which provides a simple descriptive profile and a single index value for health status.
- **EORTC QLQ-C30**: a validated questionnaire used to assess the quality of life of cancer patients
- **EORTC LMC21:** a validated questionnaire specifically for patients with liver metastases from colorectal cancer
- **Health and social care resource use**: is composed of questions related to contact with primary, community and social care services including medications, plus time off work.

Participants will complete the health related quality of life questionnaires at baseline[8] and at 3, 6, 12, 18 and 24 months post-randomisation. Participants will complete health and social care resource use questionnaires at 3, 6, 12, 18 and 24 months since randomisation, covering the period since the previous questionnaire was completed (or since hospital discharge from index treatment in the case of the questionnaire at 3 months post-randomisation).Baseline questionnaires will be completed at clinic (wherever possible[9][10]) and participants will be asked to seal the questionnaires in pre-supplied stamped addressed envelopes prior to being given to research staff. Research staff will then send the sealed envelopes to the CTRU for entry into the database.

Participant questionnaires at 3, 6, 12, 18 and 24 months post-randomisation will be received by the participants via post (these will be posted directly from the CTRU) who complete them at home and return them to the CTRU using a pre-supplied stamped addressed envelope. A thank you letter will be sent to participants by CTRU upon receipt of a completed questionnaire. Should a completed questionnaire not be received at CTRU by the required timepoint, CTRU will send a reminder letter to the participant.

The timings of completion of participant-completed questionnaires are summarised in Table 1. All participants will be followed up as per protocol until 24 months post-randomisation.

[8] Baseline questionnaires must be completed after consent and, wherever possible, prior to randomisation (where this is not possible, they must be completed prior to the participant being made aware of their randomised treatment).

[9] Where this is not possible due to clinic visit time constraints, the participant may complete their baseline questionnaire at home and return directly to CTRU using the stamped addressed envelopes, however they must remain unaware of their randomised treatment.

14 ECONOMIC EVALUATION

In the within-trial analysis, quality adjusted life years (QALYs) will be calculated for each patient based on the survival data and health related quality of life data collected during the trial. The latter will be based on the EQ-5D-5L (www.euroqol.org), which will be collected at baseline and at 3, 6, 12, 18 and 24 months post-randomisation. The within-trial cost analysis will be based on volume of resource use data collected retrospectively for each patient during the trial at 3, 6, 12, 18 and 24 months post-randomisation. Cost components included in the analysis will consist of the detailed cost of the ablation procedures (including annuitized capital costs plus consumables), and laparoscopic and open surgical resection procedures, the costs of treating the complications of these procedures, CT scans and other imaging tests, MDT meetings, costs of chemotherapy, contacts for receipt of chemotherapy, contacts and medications for treating the side effects of chemotherapy, plus other resource use associated with the cancer and its sequelae (e.g., outpatient attendances, hospital readmissions, palliative care, primary care contacts, prescribed medications, use of social services including hospice care, and time off work). The volume of resource use for each cost component will be measured directly in the trial using the Treatments data and Post-treatment data for the index treatment and the patient questionnaires for subsequent resource use; unit costs will be taken from standard published sources.

For the within-trial analysis patient-specific utility profiles will be constructed assuming a straight line relation between each of the patients EQ-5D scores at each follow-up point. The QALYs experienced by each patient from baseline to 2 years will be calculated as the area underneath this profile. Patient level resource use data will be multiplied by the unit costs and summed across all cost components to calculate total costs per patient over the two year period. Multiple imputation by chained equations will be used to deal with missing EQ-5D and resource use values. Subsequent analyses of imputed data will include variance correction factors to account for additional variability introduced into parameter values as a result of the imputation process. Cost-effectiveness will be calculated as the mean cost difference between ablation and surgical resection divided by the mean difference in outcomes (DFS/QALYs) to give the incremental cost-effectiveness ratio (ICER). Non-parametric methods for calculating confidence intervals around the ICER based on bootstrapped estimates of the mean cost and QALY differences will be used [35]. The bootstrap replications will also be used to construct a cost-effectiveness acceptability curve, which will show the probability that use of ablative therapy is cost-effective at 2 years for different values of the NHS' willingness to pay for an additional QALY, and a cost-effectiveness confidence ellipse. We will also subject the results to extensive deterministic (one-, two-way, multi-way, threshold) sensitivity analysis.

In the lifetime model cost-effectiveness will be calculated in terms of the incremental cost per QALY gained. We will undertake a review of the Cost-Effectiveness Analysis (CEA) Registry (https://research.tufts-nemc.org/cear4/) and the NHS Economic Evaluation Database (NHS-EED, www.crd.york.ac.uk/) to identify previous economic models that might be adapted. We will then develop a new cost-effectiveness model that will be populated based on available evidence, including the data collected during the trial. Following decisions about model structure, a list of parameter estimates required for the model will be developed. The specific details of the data to be used to populate the model will be determined following the development of the structure and the systematic searches of the literature to identify existing models. We will undertake deterministic and probabilistic sensitivity analysis, the latter

assuming appropriate distributions and parameter values [36]. As part of this, we will construct cost-effectiveness acceptability curves and cost-effectiveness confidence ellipses.

We will use the numerator of the ICER described above to calculate the budget impact of using ablation compared with surgical resection, multiplying the incremental cost (positive or negative) by the estimated eligible population size. We will also undertake a value-of-information trial [36]to measure the maximum amount to money the NHS should be willing to pay for additional research to reduce uncertainty regarding the use of ablation versus surgical resection in this patient group.

15 ENDPOINTS

15.1 PRIMARY ENDPOINT

The primary endpoint is disease free survival, defined as time from randomisation to the first event, which is defined as any of the following:

- Local, regional or extra hepatic/systemic recurrence of disease
- Death (any cause)

The time-to-event for patients whose treatment fails will be set equal to 0. If, according to post-intervention assessment, the index disease is deemed to have not been successfully removed/eradicated, then the treatment will be classed as having "failed".

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

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

Extra-hepatic/systemic recurrence is defined as detection of new[11] disease at any site other than the liver after successful trial intervention.

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

15.2 SECONDARY ENDPOINTS

Secondary end-points include:

- Overall survival, defined as time from randomisation to death (any cause). This will be evaluated at 2 years and 5 years.

[11] "new disease" refers to any extra-hepatic/systemic disease which was not already detected before commencement of trial treatment. For example, for participants with primary cancer in situ (i.e. patients who are stratified under "Primary cancer in situ"="Yes" at randomisation), detection of that primary cancer after successful trial intervention is not considered to be an "extra-hepatic/systemic recurrence".

- Local, regional and extra-hepatic/systemic recurrence of disease at 2 years post-randomisation.
- Disease free survival (DFS) (measured from end of intervention) at 2 years post-randomisation.
- Use of subsequent therapies within 2 years post-randomisation after treatment failure
- Health related quality of life (EQ-5D, EORTC QLQ-C30, EORTC LMC21) [31-33] at baseline, and 3, 6, 12, 18, and 24 months post-randomisation.
- Complications during treatment
- Post-treatment complications
- Length of intensive therapy unit (ITU) and inpatient stay.

End-points relating to the economic evaluation can be found described in section 14, and end-points relating to the qualitative sub-study can be found described in section 24.

16 STATISTICAL CONSIDERATIONS

16.1 SAMPLE SIZE

330 patients are required to demonstrate non-inferiority of thermal ablation with respect to resection in terms of the primary endpoint with 80% power at the 2.5% one-sided level of significance, assuming a median time to event of 14 months in the resection arm and a non-inferiority margin of 4 months and allowing for a 5% drop-out rate.

17 STATISTICAL ANALYSIS

Statistical analysis is the responsibility of the CTRU Statistician, not including the Economic Evaluation analysis (see section 14) or the analysis of the qualitative sub-study (see section 24). A full statistical analysis plan will be written before any analyses are undertaken and in accordance with CTRU standard operating procedures.

Analysis and reporting will be in line with CONSORT guidelines. Analyses will be carried out on both an intention-to-treat (ITT) basis and per-protocol (PP) basis. Non-inferiority hypotheses will be tested at the one-sided 2.5% level of significance. Superiority hypotheses will be tested at the two-sided 5% level of significance. 95% confidence intervals for parameter estimates will also be reported.

The primary analysis will assess the difference in disease-free survival. The non-inferiority hypothesis will be tested using an appropriate survival model to incorporate random effects with respect to research sites, and including adjustment for the stratification factors. The specific survival model that is most “appropriate” cannot be determined a priori – for example, the Cox proportional hazards model will be considered but will not be used if the proportional hazards assumption is violated. Patients for whom an event is not reported during their trial follow up will be censored at the last date that they were known to not have had an event.

Differences in rates such as complication rates and recurrence rates will be analysed using multi-level logistic regression incorporating random effects with respect to research site, and will include adjustment for the stratification factors.

Subgroup analysis based on the type of surgery (open or laparoscopic liver resection) and type of ablation (RFA or MWA) will be performed. If there are truly substantial differences in efficacy between types of treatment within an arm, then these subgroup analyses, whilst likely having limited precision, will give an unbiased indication of the magnitude and direction of the differences. This will allow us to explore how the treatment effect partitions into these more precise components, which will allow us to assess the validity of assumption that there is no substantial difference in efficacy between open and laparoscopic surgery, and there is no substantial difference between RFA and MWA. This will also allow us to perform sensitivity analyses using imputation methods to assess the impact of changing the proportion of each type of treatment performed within arm on the primary treatment effect estimate. This will facilitate the generalisability of our inferences to wider practice and also to potential changes in the uptake of each type of treatment over time.

Continuous measures such as length of ITU and hospital stay will be analysed using multi-level Normal-errors regression incorporating random effects with respect to research site, and including adjustment for the stratification factors. In the case of deviation from the Normality assumptions, the appropriately transformed variable will be analysed.

Exploratory analyses will be performed to assess the strength of Tumour markers as a predictor of recurrence (as defined in section 15.1).

A DMEC will be set up to independently review data on safety and recruitment. Interim reports will be presented to the DMEC in strict confidence, in at least yearly intervals. This committee, in light of the interim data, and of any advice or evidence they wish to request, will advise the TSC if there is proof beyond reasonable doubt that one treatment is better. No formal interim analyses are planned hence no statistical testing will take place until final analysis.

18 TRIAL MONITORING

Trial supervision will be established according to the principles of GCP and in-line with the NHS Research Governance Framework (RGF). This will include establishment of a core Project Team, Trial Management Group (TMG), an independent TSC and independent DMEC. A Trial Monitoring Plan will be developed based on the trial risk assessment; this may include site monitoring.

18.1 TRIAL STEERING COMMITTEE (TSC) & DATA MONITORING AND ETHICS COMMITTEE (DMEC)

An independent DMEC will be appointed to review the safety and ethics of the trial, alongside trial progress and the overall direction as overseen by the TSC. Detailed un-blinded reports will be prepared by the CTRU for the DMEC at approximately yearly intervals.

The DMEC will be provided with detailed un-blinded reports containing the following information:

- Rates of occurrence of unexpected serious complications (USCs; see section 12.1) by treatment group
- Time between randomisation and trial treatment by treatment group for each participating research site
- Rates of intra-treatment and post-treatment complications by treatment group for each participating surgeon/radiologist
- Rates of, and reasons for, treatment failure (as defined in section15.1)

Trial progress will be closely monitored by the independent DMEC, who will report to the TSC, and the overall direction overseen by the TSC (ensuring regular reports to the NIHR Health Technologies Assessment (HTA) programme).

18.2 DATA MONITORING

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until they are received, until confirmed as not available, or until the trial is at analysis.

The CTRU or Sponsor will reserve the right to intermittently conduct source data verification (SDV) exercises on a sample of participants, which will be carried out by staff from the CTRU or Sponsor. SDV will involve direct access to participant medical notes at the participating research sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

A Trial Monitoring Plan will be developed.

18.3 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by participants during the trial period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual research sites.

19 QUALITY ASSURANCE, ETHICAL CONSIDERATIONS, AND CONFIDENTIALITY

19.1 QUALITY ASSURANCE

The trial will be conducted in accordance with the principles of GCP in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework (RGF) and through adherence to CTRU SOPs.

19.2 SERIOUS BREACHES

The CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to **immediately** notify the CTRU of a serious breach (as defined in the latest version of the HRA SOP) that they become aware of. A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree-

a) the safety or physical or mental integrity of the trial subjects, or

b) the scientific value of the research.

In the event of doubt or for further information, the Investigator should contact the Senior Trial Manager at the CTRU.

19.3 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013. Informed written consent will be obtained from the participants prior to randomisation into the trial. The right of a patient to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment.

19.3.1 Ethical approval

Ethical approval will be sought through HRA. The trial will be submitted to and approved by a REC and the appropriate Site Specific Assessor for each participating research site prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, participant information sheets, consent forms and all other relevant trial documentation.

20 Confidentiality

All information collected during the course of the main trial will be kept strictly confidential. Information will be held securely on paper at the CTRU. In addition, the CTRU will hold electronic information on all trial participants. The CTRU will have access to the entire database for monitoring, co-ordinating, and analysis purposes.

The CTRU will comply with all aspects of the 1998 Data Protection Act. Operationally this will include:

- Explicit written consent from participants to record personal details including name, date of birth, NHS number.

- Appropriate storage, restricted access and disposal arrangements for participants' personal and clinical details.
- Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation.
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- Copies of participants consent forms, which will include participants names, will be collected when a participants is randomised into the trial by the CTRU. In addition participant name and address will be collected for questionnaire posting. All other data collection forms that are transferred to or from the CTRU will be coded with a unique participant trial number and will include two participant identifiers, usually the participant's initials and date of birth.
- Where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending.
- Where anonymisation of documentation is required, research sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a participant withdraws consent from further trial treatment and/or further collection of data, their data will remain on file and will be included in the final trial analysis.

Please see section 24 for further details about data collected for the part of the qualitative sub-study

20.1 ARCHIVING

20.2 Trial data and documents held by CTRU

At the end of the trial, all data held by the CTRU and all trial data will then be securely archived at the University of Leeds in line with the Sponsor's procedures for a minimum of 20 years.

20.3 Trial data and documents held by research sites

Research sites are responsible for archiving all trial data and documents (ISF and all essential documents therein, including CRFs) at the participating research site until authorisation is issued from the Sponsor for confidential destruction.

20.4 Participant medical records held by research sites

Research sites are responsible for archiving trial participant medical records in accordance with the site's policy and procedures for archiving medical records of patients who have

participated in a clinical trial. However, participant medical records must be retained until authorisation is received from the Sponsor for confidential destruction of trial documentation.

21 STATEMENT OF INDEMNITY

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

22 TRIAL ORGANISATIONAL STRUCTURE

Research sites will liaise with the CTRU for advice and support on trial set-up and operation, and submission of trial data. In turn, the CTRU will be responsible for data chasing.

22.1 RESPONSIBILITIES

The CI is responsible for the design, management and reporting of the trial.

The CTRU will have responsibility for overall conduct of the trial in accordance with the NHS RGF and CTRU SOPs.

The responsibility for ensuring clinical management of participants is conducted in accordance with the trial protocol ultimately remains with the PI at each research site.

22.2 OPERATIONAL STRUCTURE

Chief Investigator (CI): As defined by the NHS Research Governance Framework, the CI is responsible for the design, conduct, co-ordination and management of the trial.

Trial Sponsor- University College London (UCL). The sponsor is responsible for trial initiation management and financing of the trial as defined by the Directive 2001/20/EC. The sponsor delegates some of these responsibilities to CTRU as detailed in the trial contract.

Clinical Trials Research Unit (CTRU): the CTRU at the University of Leeds will have responsibility for the conduct of the trial in accordance with the NHS Research Governance Framework (RGF) and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs including randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification,

ongoing management including training, monitoring reports and trial promotion, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support ethical approval submissions, any other site-specific approvals, and clinical set-up. The CTRU will be responsible for the overall day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting, and all statistical analyses. At the end of the trial, CTRU will be responsible for archiving all data and trial data held by the CTRU in line with the Sponsor's procedures for a minimum of 20 years.

22.3 OVERSIGHT/ TRIAL MONITORING GROUPS

Trial Management Group (TMG): the TMG, comprising the CI, CTRU team, other key external members of staff involved in the trial, and a patient representative will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results. Specifically the TMG will be responsible for:

- Protocol completion
- CRF development
- Obtaining approval from the REC and supporting applications for Site Specific Assessments (SSAs)
- Completing cost estimates and project initiation
- Nominating members and facilitating the TSC and DMEC
- Reporting of complications
- Monitoring of screening, recruitment, treatment and follow-up procedures
- Auditing consent procedures, data collection, trial end-point validation and database development.

Trial Steering Committee (TSC): the TSC will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two other independent members, and a consumer representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

Data Monitoring and Ethics Committee (DMEC): the DMEC will review the safety and ethics of the trial by reviewing interim data during recruitment and follow-up. The Committee will meet annually as a minimum.

22.4 FUNDING

This project is funded by the National Institute for Health Research Health Technology Assessment Programme (NIHR HTA) - project number 13/153/04.

23 PUBLICATION POLICY

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Authorship decisions will be guided by standard requirements for authorship relating to submission of manuscripts to medical journals. These state that authorship credit should be based only on the following conditions being met (http://www.icmje.org):

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Substantial contribution to drafting the article or revising it critically for important intellectual content
- Substantial contribution to final approval of the version to be published.

In light of this, the CI, other grant co-applicants, and relevant senior CTRU staff will be named as authors in any publication, subject to journal authorship restrictions. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial. It is planned that the PIs from the top five recruiting sites will be named as authors and the investigators acknowledged as collaborators in publications..

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

On completion of the research project a draft final report will be submitted to the HTA programme (trial funder) by the CTRU, within 14 days. This will be peer reviewed and then published on the HTA website. The CTRU is obliged to provide NIHR/HTA with advanced notice of any publication relating to the trial. Copies of any materials intended for publication will be provided to NIHR/HTA at least 28 days prior to submission for publication.

24 SUB-STUDY

A qualitative sub-study will be performed in the pilot study to qualitatively explore patient and clinician acceptability of the trial and recruitment processes

24.1 Brief background

Recruitment to Randomised Controlled Trials (RCTs) with very different treatment arms can be difficult and recruitment to surgical trials is particularly challenging[37]. Surgical trials present practical and methodological challenges, including difficulties in recruitment, randomization and lack of surgical equipoise [38]. Understanding why patients do or do not participate in surgical trials is important and clinical trials have recently begun to incorporate a qualitative component to address these issues. These studies have been able to successfully identify aspects of the trial design that hindered recruitment and identifying possible solutions [37, 39]. The current trial compares thermal ablation and liver resection surgery for colorectal liver metastases so it is essential to understand and address barriers to recruitment in order to demonstrate our ability to undertake the trial.

The HTA funded STAR study [40] shows that both patient-related (difficulties of informed consent, preference for certain treatments) and clinician-related factors (concern about impact on the doctor-patient relationship and professional biases) affect recruitment. Non-participation can also be related to how the clinical trial is presented to the patient, and how the patient assimilates this information [39, 41, 42]. It is therefore important to understand how patients perceive information about potential participation and their experiences of receiving information relating to the trial.

Patients may have a strong preference for one treatment or the other and may feel uncomfortable with the randomisation process. Understanding why patients choose not to participate or do not take up their treatment allocation will be crucial demonstrating that recruiting to the phase III trial is feasible. We will explore what patients understand, perceive and feel about, how the trial was presented to them and their expectations of study burden. We will include those participants who have declined participation; those who agreed to participate in the study but do not take up their treatment allocation after being randomised into a particular study arm, and those who agree to take part. Recruitment and retention of participants is essential to demonstrate our ability to perform a definitive trial with this population, and so this work will explore the factors influencing recruitment from the patients' perspective.

We will examine clinicians' willingness to recruit to the trial and their views about the two treatments. We will discuss with them any difficulties staff experienced running the trial, for example with data collection, the timing of consent, how and who approaches patients. Understanding these issues will help us better understand the results of the feasibility trial, and identify improvements we can make to the trial design [43].

This sub-study will be run by qualitative researchers at the Leeds Institute for Health Sciences (LIHS), based at the University of Leeds, who will be responsible for all aspects relating to the sub-study.

Aims: To qualitatively explore patient and clinician acceptability of the trial and recruitment processes to assist in optimisation of recruitment and follow up strategies employed for the remainder of the trial.

Qualitative research will therefore be performed to achieve the following objectives:

1. To qualitatively explore patients and clinicians acceptability of the trial to assist in optimisation of recruitment strategies employed for the definitive trial
2. Explore reasons for participation and non-participation of eligible patients
3. Understand patients' experience of the randomisation process on decision making
4. Understand why people refuse to participate or do not take up allocated treatment
5. Patient understanding of trial materials i.e. do patients understand what will happen if they take part and do they understand what they are being randomised to
6. Acceptability of study procedures
7. Acceptability of randomisation
8. Explore clinical equipoise in the liver surgery community
9. 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

24.2 Method

Design: Semi structured interviews

Interviews with a sample of eligible patients will explore patient's perspectives of treatment, their understanding of the two treatments, reasons for taking part or refusing the trial and acceptability of randomisation between procedures.

Interviews with clinical staff at the pilot sites will explore their views about the trial, clinical equipoise and their understanding of the recruitment challenges. Semi structured interviews will be informed by a topic guide developed in conjunction with PPI representatives, clinical colleagues and informed by the literature.

Participant information sessions (recruitment encounters) will also be audio recorded to examine how information is presented, and identify issues potentially affecting trial recruitment. Although the content of information sheets are standardised, the content and quality of spoken information is often less standard and their effects on patient understanding has been shown to important [42].

24.3 Sample

A purposive sample of up to 20 patients will be recruited over 9 months from across the UK trial sites, to include the three outcomes of consent: a) participant consented and accepted treatment allocation b) participant consented to randomisation but refused the allocated treatment c) participant refused randomisation.

A purposive sample of approximately 15 health care professionals (local principal investigators, recruiters) from across the trial sites will be interviewed. Participants will be selected on the basis of their ability to shed light on the recruitment process (initial discussion, recruiter interview).

A random subset of up to 60 recruitment interviews / encounters will be selected and analysed to identify potentially directive uses of language and good practice.

24.4 Sub-study Eligibility Criteria

24.4.1 Inclusion

Patients with colorectal liver metastases considered to be suitable for liver resection who were approached for the trial and either:

- consented to participation in the trial and accepted treatment allocation
- consented to randomisation but refused the allocated treatment
- refused randomisation

Staff involved in initial discussions with patients about the trial and / or recruitment to the trial (oncologists, surgeons, research nurses, clinical nurse specialists).

All recruitment encounters will be included in the random selection for analysis.

24.4.2 Exclusion

Patients

- Unable to provide consent to research due to cognitive impairment or communication difficulties

24.5 Sample identification and consent process for patients

Patients fitting the inclusion criteria will be identified at the first encounter with their doctor/nurse to discuss the trial. An information pack will be provided by the clinical team and verbal consent to be contacted by a researcher will be sought using the expression of interest (EoI) / reply slip. This will be passed to the LIHS research team so that contact can be made 7 days later to see if the patient is interested in participating.

If patients would like time to consider participation they will be invited to return the EOI / reply slip, directly to the research team using the freepost envelope provided. The EoI will give the research team at the University of Leeds permission to contact the patient to discuss the study. Patients will also be able to telephone the researchers without returning the EoI using the contact details provided in the information pack.

After permission is given, the research team at the University of Leeds will contact the patient to discuss the study in more detail. If the patient requires more time to consider participation, they may contact the researcher at a later time to arrange an interview.

Patients may also be approached at their regular clinical or research appointment or telephoned about the study by their clinical team (if it was decided by the clinical team that it was inappropriate to discuss this research with them at their recruitment appointment(s) for the trial.

This recruitment strategy has been selected because such an approach minimises response bias and potentially increases the methodological rigour of the research [44].

Written consent will be taken prior to the interview.

24.5.1 Interview procedure for patients

In depth semi-structured interviews will be conducted with participants to explore patients perspectives of treatment and their understanding of the two treatments offered in the trial. As a key aim of the pilot study is to understand and try to address issues around clinical trial participation, reasons for taking part or refusing the trial and acceptability of randomisation between procedures will be explored as will their expectations of likely trial burden, barriers to participation and their views about randomisation.

The interview guide was developed from the existing literature and discussions with the Chief Investigator, clinicians and Patient and Public Involvement members. The interviews will be led by an experienced qualitative researcher) and conducted at a mutually convenient time and place (may be the participants home, university premises or local hospital). Since several studies [45, 46] have shown that there are no major differences in the results of telephone and face-to-face interviews, participants will also be given the option of a telephone interview to accommodate family obligations. Basic demographic information will be collected on all participants. Interviews will be audio-recorded, with the permission of the participant. Participants will be offered travel expenses if they travel to the university or hospital for their interview, but no fee will be paid for their time.

24.6 Sample identification and consent process for staff

All staff involved in recruitment process at each trial site will be invited to participate (local PI, recruiters, local clinical staff). An information pack will be sent internally / via email by the local Principal Investigator to their local staff. The pack will include a PIS, demographics form and consent form. A reminder will be sent to each site 2 weeks after the first invitation. A purposive sample will be drawn from those expressing an interest in participating.

24.6.1 Interview Procedure for staff

Interviews (telephone or face to face) will be offered to those expressing an interest. Interviews will be conducted by an experienced qualitative researcher. Written consent will be taken at the beginning of the interview from anyone not returning their form prior to the interview. A topic guide will be used to guide the discussion. This has been informed by existing literature (e.g. [47]) clinical input and our PPI members, to include: their views about the trial (beliefs about, and attitudes towards the interventions), clinical equipoise and their understanding of the recruitment challenges (barriers to recruitment and training needs). The interviews will be

audio-recorded with permission of the participants. Participants will be reminded of their right to withdraw from the study at any time and request withdrawal of their data. Participants will be asked to indicate on their consent form if they would be willing to be contacted after the interview to answer questions which may emerge during the analysis, or to explore issues that emerged in the interviews in more depth. These interviews may be face-to-face or by telephone, and further participation will be optional.

24.7 Sample identification & consent process for recruiter meetings

All recruitment encounters with patients will be recorded routinely for monitoring and training purposes. For example, the first contact with patients to discuss the trial and any following recruitment meetings / clinic appointments where the trial might be discussed will be audio recorded with consent from the patient and staff member. The aim of the recording is to capture examples of good practice which can be shared with others, as well as examples which might identify areas for training. Health professionals involved in recruitment for the trial will wear a visible microphone on their lapel / use visible audio recording equipment throughout their meeting with the patient. At the opening of the meeting the health professional will emphasise that the recording is focussing on the professionals' and is not concerned with details relating to individual patients. At the opening of the meeting and to avoid a 'break in the flow' of conversation the health professional will seek verbal consent to record the interaction before talking about the study. For example, "Can I tell you about a clinical study that you are eligible to take part in?" If the patient is agreeable to finding out about the study: "Part of the study involves researchers listening to how I present the information to you, are you happy for me to take an audio recording of our conversation?" This procedure was reported to be very successful in capturing the critical exchange of information between patients and health care professionals within a number of trials, for example the ProtecT trial [42], [47], [48],[49].

Written consent to record recruitment encounters will be obtained at the end of the meeting with their doctor.

Recording will be terminated during interactions with those patients who decline consent to be recorded. Recordings will be destroyed for those patients who give verbal consent to be recorded but no written consent is obtained, and professionals and patients will be entitled without question to withdraw the contents of selected encounters from analysis should they wish; these can be destroyed by the participant prior to data transfer to the research team, or on request at a later date.

24.8 Data analysis

All interviews will be professionally transcribed verbatim and managed within NVivo. The data will be analysed using thematic analysis [50, 51] and coded independently by two researchers for emerging themes who will then compare codes and themes and resolve any disagreements by consensus. The analysis will be further refined by using constant comparison and contrastive approach, and looking for negative cases. A subset of up to 60 recruitment interviews will be analysed using content analysis to identify potentially directive uses of language and good practice.

24.9 Outputs

- An understanding of why patients do or do not participate in surgical trials
- An understanding of barriers to recruitment
- Identification of aspects of the trial design that have hindered recruitment in the pilot phase
- Identification of possible solutions to recruitment difficulties for the main trial.
- Training will be delivered to surgeons and oncologists through the use of written materials which would be delivered within MDT sessions and face-to-face training sessions for all surgeons and oncologists who decide on the treatment of patients i.e. people who play an important role in the selection of patients for the trial) and those involved in the recruitment process i.e. research nurses, clinical nurse specialists' who might be involved in delivering patient information sessions, recruitment meetings (consent & randomisation). The training package will be informed by the qualitative work and existing literature on improving recruitment to surgical RCTs. It will incorporate presentations and role play exercises to allow staff to practice their communication skills and receive feedback. The purpose of the training is to improve buy in from MDTs and good collaboration between surgeons and oncologists in how & when the study is presented to patients.

24.10 Ethical issues

24.10.1 Potential distress

Recent evidence suggests that qualitative interviewing, even when using unstructured interview guides (i.e. those which are not pre-approved by the ethics committees) does not have long-term negative effect which would require psychological treatment. In fact, the participants are far more likely to experience relief after discussing distressing experiences [52]. However, it is nevertheless possible that the participant will experience distress while remembering the nature of their illness. To address this issue we have ensured that the researchers have considerable experience in qualitative research in healthcare and working with vulnerable patient populations and will be able to handle these issues sensitively.

If the researcher is not able to address participant's distress then the patient will be referred to the participating hospital's counselling service.

24.10.2 Confidentiality

We will be mindful of protecting participant confidentiality at all times. All audio recordings of interviews with patients and staff will be stored on the University of Leeds secure (S) drive and accessed only by researchers involved in data analysis. Audio recordings collected during recruitment encounters will be uploaded to a Trust NHS secure server immediately after recording, or as soon as is possible. The digital file will then be permanently deleted from the recording device. The uploaded digital file will then be transferred via encrypted email - nhs.net to nhs.net to the research team at Leeds. Through liaison with trial staff the researcher will

have prior notification of when to expect a transfer of the data (digital file) and to download as soon as is possible and store on the secure server at the University of Leeds.

Alternatively the uploaded digital file can be transferred onto an encrypted memory stick (provided by the research team) and posted using recorded delivery – to be signed for by the researcher only. Through liaison with staff the researcher will have prior notification of when to expect a transfer of the data (digital file).

During transcription, all the personal data in the transcripts will be removed and/ or anonymised so the participants' identity will be protected. The participants will then be referred to by a pseudonym (which can be chosen by the participant) which will bear no resemblance to their identity, hospital number, DOB or similar. Participants will be asked to consent to direct quotes. The audio recordings will be retained until after analysis is completed as nuances in what a person says (and how) can be lost during transcription, and listening to the tape provides contextualisation and helps the researcher to remain grounded in the data. They will then be destroyed.

Any paper documents (e.g. consent forms, demographic questionnaires etc.) and any information about the participant will be kept in a locked cabinet at Leeds Institute of Health Sciences, University of Leeds. All electronic information will be stored on the University of Leeds' computers which are password protected. The file in which codes are linked to patients' names will only be stored on a password protected computer on a secure network.

We are aware that some patients might discuss circumstances of potential conflict or tensions with their healthcare providers. In order to protect the anonymity of such participants who might continue to see these professionals but might be identified by such incidents and circumstances, specific instances will be summarised and details changed for the training materials. However, such incidents might be discussed in academic outputs as sufficient time will lapse for such incidents no longer to be relevant.

All data will be archived in accordance with University of Leeds procedures.

24.10.3 Informed consent

The patients will be required to sign a consent form prior to getting involved in the study. Those unable to consent for themselves will be excluded from participating.

24.10.4 Lone worker policy

Interviews are being conducted on a one-to-one basis between a participant and the researcher. As the participants can choose the time and place of the interview and can opt to be interviewed in their own homes, there is some risk to the researcher. For this reason the researcher from University of Leeds will follow the University's "Lone worker" policy.

24.10.5 Estimated Timelines

Time frame: During 12 months pilot phase (anticipated dates – October 2016 – August 2017).

25 ABBREVIATIONS USED

ACRONYM	DEFINITION
ALPPS	Associating Liver Partition and Portal vein Ligation for Staged hepatectomy
APL	Authorised personnel log
ASA	American Society of Anesthesiologists
CEA	Carcinoembryonic antigen
CEA	Cost-Effectiveness Analysis
CI	Chief Investigator
CLM	Colorectal liver metastases
CRF	Case Report Form
CTRU	Clinical Trials Research Unit
CVA	Cerebrovascular accidents
DFS	Disease free survival
DICOM	Digital Imaging and Communications in Medicine
DMEC	Data monitoring & ethics committee
ECG	Electrocardgiogram
EOI	Expression of interest
EORTC	European Organisation for Research and Treatment of Cancer
FBC	Full blood count
GCP	Good clinical practice
HIFU	High intensity focused ultrasound
HPB	Hepato-Pancreato-Biliary
HRA	Health Research Authority
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
ISF	Investigator site file
ITT	Inention-to-treat
ITU	Intensive therapy unit
LFT	Liver function test
LIHS	Leeds Institute of Health Sciences
MDT	Multi-disiplinary team
MWA	Microwave ablation
NHS	National Health Service

NHS-EED	NHS Economic Evaluation Database
NIHR	National Institute for Health Research
ONS	Office of national Statistics
PE	Pulmonary embolism
PFS	Progression free survival
PI	Principal Investigator
PIS	Patient information sheet
QALY	Quality adjusted light years
RCT	Randomised controlled trial
REC	Research ethics committee
RFA	Radiofrequency ablation
RGF	Research governance framework
SC	Serious complication
SDV	Source data verification
SSOP	Site standard operating procedure
TMG	Trial management group
TSC	Trial steering committee
U&E	Urea and electrolytes
UCL	University College London
UoL	University of Leeds
USC	Unexpected serious complication

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APPENDIX 1: Clavien-Dindo Classification of Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative[12] course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III Grade IIIa Grade IIIb	Requiring surgical, endoscopic or radiological intervention Intervention not under general anesthesia Intervention under general anesthesia
Grade IV: Grade IVa Grade IVb	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management Single organ dysfunction (including dialysis) Multi organ dysfunction
Suffix “d”	If the patients suffers from a complication at the time of discharge, the suffix “d” (for ‘disability’) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

‡ brain hemorrhage, ischemic stroke, subarrachnoidal bleeding,but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.

[12] For participants in the ablation arm, “post-operative” should be interpreted as post-ablation