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Liver resection surgery vs. thermal Ablation for colorectal liVer metAstases

LAVA: Liver Resection Surgery Versus Thermal Ablation for Colorectal LiVer MetAstases

PARTICIPANT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT

A large-print version of this sheet is available on request.

You have been invited to take part in a research study called "LAVA"

Before you decide if you want to take part, we would like to explain why the research is being done, how we will use the information we have about you, and what the study will involve.

Please read this information carefully, and discuss it with others if you like. Ask us if anything is unclear, or if you would like more information.

Once you have read this information, your doctor or nurse will talk to you about the study again and you can ask any questions you like.

- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Please take time to decide whether or not you wish to take part.

How to contact us

If you have any questions about this study, please talk to your doctor at

<<Enter PI, nurse name >>

<< Contact details for site>>

Thank you for reading this information sheet.

The trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project no. 13/153/04)

Part 1

What is the purpose of the study?

About 41,000 people develop bowel cancer each year in the UK. About 30% of people have bowel cancer spread to the liver (colorectal liver metastases). Partial removal of the liver (liver resection surgery) is effective in improving the life expectancy in people with colorectal liver metastases (CLM).

Liver resection is a major operation with high complication rates. At present, liver resection is the standard treatment in people below 70 years of age who are otherwise well; however the treatment of elderly people, those with additional medical problems (such as severe heart or lung disease) and those in whom there is extensive spread of cancer within the liver is less clear.

Ablative treatments (destruction of cancer using methods other than surgery such as heat, extreme cold, or electricity) offer an alternative to surgery in patients with colorectal liver metastases. Ablation therapy can avoid the risks of major surgery and some studies have shown that ablative treatment is as good as surgery in terms of removing cancer. However there is concern from other studies that the local recurrence rate may be higher and the cure rate lower after ablation than with surgery. Thus, there is a great deal of uncertainty as to which treatment (surgery or ablation) is better in people with CLM who are high risk for surgery. The LAVA trial has been designed to find out if thermal ablation is as good as liver resection for people with CLM in people who are high risk for surgery.

Why have I been chosen?

You are being asked to take part in the LAVA trial because you have been diagnosed with colorectal liver metastases and you are considered high risk for surgery either because of the extent of cancer deposits in the liver or because of a high anaesthetic risk due to your age or other health conditions that you have.

The LAVA trial aims to recruit 330 patients like you.

Do I have to take part?

No, your participation in the LAVA trial is voluntary and you may withdraw your consent to take part at any time, without giving us a reason.

If you decide to take part you will be given this information document to keep. You will be asked to sign a consent form, but you are still free to withdraw at any time and without giving a reason. If you decide not to take part, your doctor or nurse will be happy to talk through the alternative options. Your treatment and care will not be affected in any way if you decide not to take part in this trial.

If I want to, will I definitely be able to take part?

Unfortunately, no. Although your doctor or nurse thinks that you might be suitable to take part, they will still need to carry out some tests and ask you some questions to make sure that you are suitable. These are known as "screening tests" and are described below. If the eligibility screening tests show that it is not appropriate for you to take part in LAVA, your doctor will discuss your alternative treatment options with you.

What will happen to me if I take part?

The best way of finding out whether the new treatment (thermal ablation) is as effective as standard treatment with liver resection is in a randomised trial. 'Randomised' means that a computer will allocate you randomly (as if by the roll of dice) to receive either thermal ablation or liver resection surgery. Neither your doctor nor you will choose which treatment you receive. In this way, a fair comparison can be made.

Although your clinical team thinks you might be suitable to take part, they may still need to ask you some questions to make sure you are suitable, in addition to carrying out some "screening tests". For this trial they are tests that you would have in usual clinical practice, i.e. there are no additional or special tests purely because of taking part in this trial.

- **Screening tests**

- The first tests will be the screening tests. These are routine tests for anyone receiving treatment for colorectal liver metastases at your hospital. Your clinician will be able to get some information about you from your medical notes, but may need to ask you questions about your medical history and medications to see if you are suitable for surgery or thermal ablation.

- In addition to asking you questions about your medical history, additional tests will be performed. These will be aimed at staging the cancer, i.e. determining the extent of the cancer. using scans such as CT or MRI (magnetic resonance imaging) and determining your general fitness, which usually depends upon your age and presence of other health conditions such as lung disease or heart disease. If the CT scan or MRI scan is older than 6 weeks prior to treatment, it may be repeated as part of routine clinical care so that the latest information on the extent of disease is available to the doctor treating you. The tests that you undergo to test your general fitness depends upon the health condition that you have and the local policy.

- **Baseline (before your treatment)**

Once your screening tests have been performed and it is confirmed that you able

to take part in LAVA, you will be asked to fill in a questionnaire booklet about your health-related quality of life/how you are feeling. This would be completed at the time of your clinic visit and may take around 10 to 15 minutes of your time.

- **Treatment**

You will receive either liver resection or thermal ablation (described in more detail in the following sections)

- **Trial follow-up**

You will be asked to come in for clinic visits and trial data will be collected from you at 3, 6, 12, 18, and 24 months after you enter the trial.

In addition to the visits to hospital above, you will be asked to complete questionnaires about your quality of life and about visits/phone calls to health professionals (eg your GP/practice nurse). Some of these questionnaires will be given to you in clinic, whilst others will be posted directly to you. These might take around 20 to 30 minutes of your time in each case.

At approximately 5 years after recruitment into the trial finishes, your health status will be obtained from standard NHS registries.

What is the standard treatment?

Liver resection is carried out by a specialist liver surgeon usually by open surgery and occasionally by laparoscopic surgery (key-hole surgery) depending on the site and extent of the tumours in the liver. Surgery will be under general anaesthesia. Surgery usually takes 3 to 6 hours depending upon the extent and location of the tumour. After the surgery you will stay in hospital for about a week until you are fully mobile, eating and drinking. Some patients may require two liver operations on the same admission to fully remove extensive cancers. This is to allow a short period between operations for the liver to recover. The type of surgery and the requirement for additional procedures are not determined as part of the trial or the 'randomisation' and will be determined by the individual surgeon according to local policy. In other words, the randomisation will determine whether you undergo surgery or ablation but the surgery planning will be performed by your surgeon.

What are the new treatments?

Thermal ablation destroys the liver cancers using a needle that heats the cancer deposits until they are destroyed. Two methods are in current practice, radiofrequency ablation (RFA) and microwave ablation (MWA). At present, there is no strong evidence favouring one method of thermal ablation over another. Thermal ablation is usually performed by a radiologist under general anaesthesia. The procedure is usually carried out by introducing the ablation needle through the

skin into the liver. It can also be carried out at open or laparoscopic surgery. The duration of thermal ablation mainly depends upon the type of thermal ablation (RFA or MWA) and the number of cancer deposits. It usually takes 1 hour to 3 hours to complete. After the ablation most patients remain in hospital overnight although day surgery procedures can be performed.

The type of ablation and the number of sessions is not determined as part of the trial or the 'randomisation' and will be determined by the individual radiologist according to local policy. In other words, the randomisation will determine whether you undergo surgery or ablation but the ablation planning will be performed by your radiologist.

How long does treatment go on?

Liver resection surgery usually involves a 7 to 10 days stay at hospital. A small proportion of people may need to have the surgery carried out over two operations.

Thermal ablation involves overnight stay at hospital, although sometimes you may be discharged on the same day. In some cases, it may be necessary to carry out further sessions of ablation, these would usually be carried out around 4 to 6 weeks later.

You will be asked to come in for clinic visits and data will be collected from you at 3, 6, 12, 18 and 24 months after you enter the trial.

What if the treatment doesn't help?

If there is evidence of cancer remaining after the trial treatment the further treatment options will be considered and discussed at the specialist multi-disciplinary cancer meeting who will advise you on further treatment.

Unwanted effects of treatment

There are recognised complications associated with any operation/ablation treatment. Recognised complications of both liver resection surgery and thermal ablation are listed below. These are only complications which may occur; we are not expecting them all to happen to you. These are also only examples and not an exhaustive list.

Liver resection surgery:

Complications following surgery include leakage of bile, bleeding, infections, or lung collapse. Complications occur in about 40% of people. Complications result in death in 3-4% of patients within 3 months of surgery.

Thermal ablation:

Complications include bleeding, bile duct injury, blood vessel thrombosis, liver abscess, other infections and lung collapse. Complications occur in 5-10% of individuals

and result in a 0.2% to 0.3% risk of death i.e. 2 or 3 in a 1000, i.e. about 10 fold fewer compared to surgery

Pregnancy: It is important to tell your clinical care team if you are pregnant or become pregnant as this may affect your care.

Ionising Radiation

You will be required to have a CT scan at the start of the trial and at 3, 6, 12, 18 and 24 months after entering the trial. Participants in the thermal ablation arm will also have CT scans at the end of and 4 to 6 weeks after each ablation session. You may also have a coronary angiogram as part of your baseline assessment.

The CT scans and coronary angiogram (if you have one) are all part of your routine care. If you take part in this study you will not undergo any additional CT scans or angiograms. These procedures use ionising radiation to form images of your body and provide your doctor with other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. The chances of this happening to you are the same whether you take part in this study or not.

How is my condition monitored?

Participating in the LAVA trial will not affect how your condition is monitored or other treatment you receive for it. Your disease will be monitored by regular visits to your clinical team. The follow-up visits required for the trial are similar to what would normally be done. Clinical data about your disease and any complications that occur will be collected at the time of the treatment, and at 3, 6, 12, 18 and 24 months from trial entry. You will be asked to fill in questionnaires about your quality of life before your treatment (baseline) and at 3, 6, 12, 18 and 24 months from trial entry. The questionnaires are not part of routine clinical care and are completed for the purpose of the trial.

What are the possible disadvantages/ risks of taking part?

Your clinician has recommended that you receive treatment for your liver cancer. The most common treatment for people like you is liver surgery. Surgery is chosen despite the increased death rate and complication rates and availability of thermal ablation expertise in the hospital. This is because of lack of information on the outcome of ablation therapy. Studies comparing surgery and thermal ablation give mixed results regarding which treatment is better and do not include the same type of people. This is

the first study that is aimed to determine which is better once and for all. If thermal ablation provides equivalent or better survival than surgery, then you (if you undergo ablation) and people like you will benefit because of a less invasive procedure. On the other hand, if thermal ablation does not provide equivalent survival as surgery, there is a chance that the cancer can recur earlier.

What are the possible benefits of taking part?

If thermal ablation provides equivalent or better survival than surgery, then you (if you undergo ablation) and people like you will benefit because of a less invasive procedure. The information gained from the trial will be helpful in guiding clinicians as to the best approach for the treatment of colorectal liver metastases in other high risk patients and may suggest that ablation treatment should be offered to other groups of patients who are routinely offered surgery. You will be monitored regularly and closely throughout the study.

What if something goes wrong?

As with any treatment, your clinical team aim to ensure that any risks are kept to a minimum. We have no reason to believe that thermal ablation is less effective that liver resection surgery for more high risk patients but we cannot be 100% sure that this is the case. Similarly, we cannot be sure that liver resection surgery is better than ablation. The Trial Management Group, the independent oversight committees will closely monitor the study on an on-going basis so that if there are any problems, they will be detected as soon as possible so that the trial can be changed or stopped if necessary. If you experience problems, you must report these to your study nurse or doctor.

What happens when the research study stops?

At the end of the trial, your clinical team will discuss available ongoing treatment options.

Will my taking part be kept confidential?

If you decide to participate in LAVA, the information collected about you will be handled strictly in accordance with the consent that you have given and also the 1998 Data Protection Act. Please refer to Part 2 for further details.

Contact Details

If you have any further questions about your illness or clinical studies, please discuss them with your doctor. You may also find it helpful to contact Macmillan Cancer Support, an independent cancer information charity (freephone: **0808 808 00 00**; address: 89 Albert Embankment, London,

SE1 7UQ; website www.macmillan.org.uk) or CancerHelp, an information service about cancer and cancer care for people with cancer and their families by Cancer Research UK (Tel: 020 7061 8355; website www.cancerhelp.org.uk). If you would like further information about clinical research, the UK Clinical Research Collaboration (a partnership of organisations working together on clinical research in the UK) have published a booklet entitled 'Understanding Clinical Trials'. Contact UKCRC: Tel: 0207 670 5452; website www.ukcrc.org

This completes Part 1 of the Information Sheet. If the Information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

Sometimes during the course of a study, new information becomes available. Over the course of this trial new methods of ablation and new surgical techniques may become available. If there is evidence that they are effective then they will be included as treatment options in this trial. You will be free to withdraw from the trial at any time.

What will happen if I don't want to carry on with the trial?

If you withdraw consent from further trial treatment, information will still be collected about you and will be included in the final trial analysis, unless you request otherwise. If you withdraw consent for further data collection, your initial data will remain on file and will be included in the final trial analysis. In line with Good Clinical Practice guidelines, at the end of the trial, your data will be securely archived for a minimum of 20 years. Arrangements for confidential destruction will then be made.

Who has organised, reviewed and funded the research and who will be supervising it?

The LAVA trial is being organised by University College London (UCL) and the University of Leeds through the Clinical Trials Research Unit (CTRU). The trial has been reviewed by an ethical committee and the Research and Development Department situated at your hospital. The trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project number 13/153/04). To have obtained funding by the NIHR, the trial had to go through review by experts who felt this trial to be of relevance and importance to patients and NHS. An independent Data Monitoring & Ethics Committee (DMEC) and Trial Steering Committee (TSC) will be reviewing the trial data on a regular basis to monitor the ethics, safety and progress of the trial.

What if there is a problem?

We do not expect anything to go wrong, but if a medical emergency related to your treatment for this trial occurs whilst you are at home, you should initially try to contact the hospital where you received your treatment. If this is not possible you should go to the Accident & Emergency (A&E) department at your local hospital. If you are unable to get to the hospital, you should contact the emergency on call GP.

Complaints

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this trial, the normal National

Health Service (NHS) complaints mechanisms are available. Your clinical team will give you further information if necessary

Harm

Every care will be taken in the course of this clinical trial. However, in the unlikely event that you are injured as a result of the managing organisation (University College London), compensation may be available and you may have to pay your related legal costs. Your hospital where you receive your treatment has a duty of care to you whether or not you agree to participate in the trial and the University College London accepts no liability for negligence on the part of your hospital's employees. If you wish to complain about any aspect of the way you have been treated please contact your research doctor in the first instance.

Any claims will be subject to UK law and must be brought in the UK.

If you have private medical insurance, you should tell your insurer that you are taking part in research. They will let you know if it affects your policy.

Will my taking part in this trial be kept confidential?

If you decide to participate in the LAVA trial, the information collected about you will be handled in accordance with the consent that you have given and also the 1998 Data Protection Act. The information needed for trial purposes will be collected on paper forms and sent (usually using standard Royal Mail post but in some cases by fax or email) from the hospital to the Clinical Trials Research Unit (CTRU) at the University of Leeds. You will be allocated a trial number, which will be used along with your date of birth and initials to identify you on each paper form. Your full name will be included on your consent form and a copy of this will be sent to the CTRU. In addition your full name and address will be sent to CTRU by fax or post or email to enable the CTRU to send quality of life questionnaires to your home. Every effort will be made to ensure that any further information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it; this information will usually be removed by a member of the trial team at your hospital, but may also be removed by the CTRU upon receipt.

Your data will be entered onto a secure database held at the CTRU in accordance with the 1998 Data Protection Act.

Your healthcare records may be looked at by authorised individuals from the research team, University College London (the trial Sponsor), the University of Leeds Clinical Trials Research Unit (CTRU) or the

regulatory authorities to check that the trial is being carried out correctly.

The information collected about you may be shared with other research teams to answer new research questions in the future. Wherever possible, information will be anonymised (for example; your full name will not be disclosed)

Your name, date of birth, and NHS number will be submitted to standard NHS patient registries e.g. Office of National Statistics (ONS) held at the NHS Health and Social Care Information Centre, and the UK Cancer Registry. This is so that information held and maintained by the Health and Social Care Information Centre and other central UK NHS bodies may be used to help provide information to the CTRU about your health status if necessary.

- Your data may be passed to other organisations participating in this trial (possibly in other countries i.e. the Netherlands where the data protection standards and laws are different to the UK) to monitor the safety of the treatment you are receiving; this data will have your name removed.

- CT scans for selected participants in the trial will be sent for central review to ensure that results / reports are consistent across hospitals. These will be sent via standard hospital processes (such as NHS electronic transfer, Royal Mail or courier). Wherever possible, this data will be anonymised and your name removed

Involvement of the General Practitioner/Family Doctor (GP):

Your GP, and the other doctors involved in your healthcare, will be kept informed of your participation in this trial.

What will happen if I lose mental capacity during the trial period?

This is expected to be a very rare occurrence. It could happen to any patient whether or not they are a participant in this trial, for example due to a complication of an operation (e.g. a significant stroke) or due to an entirely separate event (e.g. a head injury). If this did occur, no further trial treatment would be given and data collection for the trial would not continue. Information included up until this point will remain on file and will be included in the analysis.

What will happen to the results of the research trial?

When the trial is complete the results will be published in a medical journal, but no individual participants will be identified. The results may also be summarised on the internet- these results will not identify any individual participants If you would like to

obtain a copy of the published results, please ask your doctor.

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Participant ID:	Initials:
Date of Birth:	NHS/Hospital Number:
ISRCTN:	Principal Investigator:

LAVA
Liver Resection Surgery Versus Thermal Ablation for Colorectal LiVer MetAstases

PARTICIPANT CONSENT FORM

Please initial each box

1. I confirm that I have read and understand the information sheet for the above trial and have had the opportunity to ask questions ☐

2. I understand that my participation in this trial is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. I understand that even if I withdraw from the above trial, the data and samples collected from me will be used in analysing the results of the trial and in some cases further information about any unwanted effects of my treatment may need to be collected by the trial team. ☐

3. I understand that my healthcare records may be looked at by authorised individuals from the trial team, regulatory bodies or Sponsor in order to check that the trial is being carried out correctly. ☐

4. I agree to allow any information or results arising from this trial to be used for healthcare and/or further medical research upon the understanding that my identity will remain anonymous wherever possible. ☐

5. I understand that data may be passed to other organisations participating in this trial (possibly in other countries i.e. the Netherlands where the data protection standards and laws are different to the UK) to monitor the safety of the treatment I am receiving ☐

6. I understand that the information held and maintained by the Health and Social Care Information Centre and other central UK NHS bodies may be used to help provide information about my health status. I agree for my details (which will include my name, date of birth, NHS number to be submitted to these bodies so that information about my health status may be obtained by the CTRU if necessary. ☐

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7. I understand that my full name and address will be provided to CTRU to allow quality of life questionnaires to be posted directly to me ☐

8. I agree to a copy of this Consent Form being sent to the CTRU. ☐

9. I agree that my GP, or any other doctor treating me, will be notified of my participation in this trial. ☐

10. I understand that if during the trial my clinical care team determine that I have lost capacity to provide informed consent, no further trial treatment would be given. I agree that information collected up until this point will remain on file and will be included in the analysis. ☐

11. I agree to take part in the trial. ☐

Patient:

Signature……

Name (block capitals)……

Date……

Investigator:

I have explained the trial to the above named patient and he/she has indicated his/her willingness to participate.

Signature……

Name (block capitals)……

Date……

(If used)Translator:

Signature……

Name (block capitals)……

The trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project no. 13/153/04)

Date……

(1 copy for patient; 1 for the CTRU; 1 held in patient notes, original stored in Investigator Site File)

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