**Carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis**

**CALIBRE**



**PATIENT INFORMATION SHEET**

**We would like to invite you to take part in our research study**

You are being asked to consider taking part in a research study.Before you decide, we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions. You can talk to others about the study if you wish. Please ask us if there is anything that is not clear.

**Key points about this research:**

* *Variceal bleeding is a serious complication of liver cirrhosis.*
* *Patients with liver cirrhosis and medium to large oesophageal varices need treatment with medicines known as beta-blockers or endoscopic treatment with variceal banding to lower the risk of variceal bleeding.*
* *We do not know which treatment is better and this trial is being conducted to find this out.*
* *This study will randomly assign participants to either carvedilol or variceal banding.*
* *Our aim is to improve the care of patients with liver cirrhosis and oesophageal varices.*

**What is the purpose of the study?**

People with long standing liver disease called cirrhosis (scarring of the liver) can develop enlargement of veins in the gullet (food pipe) known as ‘oesophageal varices’. Patients with medium to large oesophageal varices have a 1 in 3 chance of these veins bleeding. In very severe cases, this could result in death. It is therefore important to lower the risk of this bleeding. At present, all people with medium to large oesophageal varices are offered one of two treatments to lower the risk of bleeding:

1. **Beta-blocker drugs**

Beta-blockers slow down the heart rate and lower blood pressure. The drugs currently prescribed to treat oesophageal varices are carvedilol, propranolol or nadolol. All of these drugs lower pressure in the varices which reduces the risk of bleeding.

Carvedilol is a beta-blocker that is used to treat high blood pressure and some forms of heart disease. Research studies have shown the drug to be also very effective at lowering the pressure in varices in the gullet. It is better than propranolol at lowering the pressure in the veins (the lower the pressure, the lower the risk of bleeding). Nadolol is similar to propranolol but is not commonly prescribed in the United Kingdom. Approximately 50% of patients experience some side effects with carvedilol as detailed later. Patients taking beta-blockers do not require further endoscopies to check on their varices unless there is a change in the clinical condition e.g. variceal bleeding.

1. **Variceal banding**

A flexible tube (endoscope) with a miniature video camera and carrying a rubber ring is passed through the mouth to the gullet. An enlarged vein can be tied off with the rubber ring. This procedure does not involve surgery and is normally done under sedation. Patients are usually allowed to go home on the same day. On average up to five endoscopy sessions, at approximately monthly intervals will be required to treat all of the varices. Subsequently, regular endoscopies to check the varices are done less frequently, and eventually annually.

Some research studies suggest that banding may be more effective than beta-blockers in lowering the risk of variceal bleeding, but other studies suggest that this is not the case. However, all of these studies have been small and we still do not know which treatment is best for reducing the risk of bleeding. We need to do a study to compare carvedilol with banding in people with cirrhosis who have medium to large varices that have never bled.

**Why have I been invited? Can I say no?**

You have been invited because you have liver cirrhosis and fall into one of two groups of patients:

* You have already had an endoscopy which shows medium or large oesophageal varices that have not bled.
* You are about to have an endoscopy to check for varices as part of your normal care.

We are aiming to recruit about 2630 patients over the course of the study. If you are invited (ie meet the criteria for the trial), it is up to you to decide whether or not to take part.

If you do decide to take part, we will ask for your consent and you will be given this information sheet and a copy of the consent form to keep.

We will either take your consent, in person during your hospital visit or we will contact you to do so by telephone or video call. If we take your consent in person, then we will ask you to sign the consent form. If we take your consent over telephone or video call, we will ask you the questions and then sign the consent form on your behalf in the presence of a witness. In both cases, you will receive a copy of the fully completed consent form.

Your consent form will stay on record in your study file and in your medical records and be available for review by the study monitors. A copy will also be held at Birmingham Clinical Trials Unit, University of Birmingham.

If you decide not to take part, your normal treatment will not be affected in any way and you will continue to be cared for by your normal care team who will ensure that you receive treatment for the varices with either beta-blockers or variceal banding.

**Are there any benefits to taking part?**

Although there may be no direct benefits to you for taking part in this study, in the future the results of the trial will lead to the best treatment being offered to prevent bleeding in patients with liver cirrhosis and medium or large oesophageal varices.

**What will happen to me if I take part?**

Sometimes we don’t know which way of treating patients is best. To find out, we need to compare different treatments by putting patients into groups with each receiving a different treatment. To make sure the groups are the same to start with, each patient is put into a group by chance (randomly). Once the treatment is assigned, you and your doctors will know which treatment you are given. The groups are selected by a computer, which has no information about the individual. Patients in each group then have a different treatment and these are compared. In this study you will have a one in two chance of either treatment (like flipping a coin). You will be assigned to receive therapy with either carvedilol tablets or variceal banding.

If you have already had an endoscopy which showed medium or large oesophageal varices that have not bled, you will be entered into the study if you give consent to take part.

If you are about to have an endoscopy to check for varices as part of your normal care, you will consent for your routine endoscopy and will be asked if you are willing to give consent to be entered into the study (see below). If you have also consented to enter the study and the endoscopy shows medium or large varices, you will be randomly allocated to either undergo variceal banding or be treated with a beta-blocker.

Once treatment is started, it will be continued for at least one year (unless any problems arise or you decide to withdraw from the study).

A summary of the trial schedule is illustrated below.



**Pregnancy**

It is possible that if carvedilol is given to a pregnant woman it will harm the unborn child. Pregnant women must therefore not take part in this study and neither should women who plan to become pregnant during the study. Women who could become pregnant must use barrier contraception during the course of the study. If you find you have become pregnant while taking part in this study, you should immediately tell the research doctor. We will need to follow you up during your pregnancy and information about the outcome of your pregnancy will be collected from yours and your baby’s medical notes. There is no risk to children born to fathers taking this medicine.

**How many visits are there and how long will it take?**

All patients who take part in this trial will be seen as is usual clinical practice either in the clinic or over telephone/ video conference, every few months to assess well-being and to look for untoward effects.

Patients who are receiving treatment with carvedilol will also be reviewed (either in clinic or by telephone or video conference consultation) two weeks after the start of treatment to make sure that there are no untoward effects. Should unacceptable side effects develop the treatment will be modified or stopped and an alternative offered. There are no special life style restrictions needed if you take part in this trial, and other medications should be continued as usual.

Patients who are receiving variceal banding will have the procedure done as described on page 2.

**How will I receive the medications?**

If you are randomised to carvedilol, you will be given a prescription following your diagnostic endoscopy and we will supply you with enough medication from the hospital pharmacy for the first few weeks. Once you are stable on your treatment, you can receive prescriptions for the medication from your GP in the normal way.

You should take the study medication regularly as directed and continue all other regular medication.

**Are the treatments and tests safe?**

Variceal banding has been used for nearly 30 years and is generally very safe. As banding is an endoscopic procedure about 1 in 10 patients may experience discomfort and find it difficult to tolerate the procedure. Infrequent complications include bleeding affecting about 1 in 20 patients, and a very small risk of causing narrowing of the gullet making it difficult to swallow or causing a tear in the gullet (perforation).

Carvedilol is a medication that was initially developed to treat high blood pressure and some forms of heart disease. As with any drug, there are potential minor side effects which affect around half of patients, but serious complications are very rare. The side effects of carvedilol which can be difficult to tolerate in about 1 in 10 patients include: shortness of breath, low blood pressure causing dizziness, and upset stomach. Other less common side effects include abnormal vision, bradycardia (slow heart rate), asthenia (fatigue), and impotence. Your doctor will carefully monitor any side effects and make changes where required.

It is important that medium to large varices are treated so if you are not able to tolerate variceal banding or carvedilol you will be offered an alternative treatment.

All the tests you will receive and procedures that will be undertaken are part of normal clinical care for patients with oesophageal varices.

There will be an independent safety committee that will oversee the trial.

**What happens when the research study stops?**

After the study finishes, your clinical care will revert to the current standard care for patients with cirrhosis and medium to large oesophageal varices that have not bled.

**What if new information becomes available?**

Sometimes we get new information about the treatments being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

**What will happen if I don’t want to carry on?**

You can withdraw from the study at any time without giving a reason. However, we would like to keep in contact with you to let us know your progress. Information collected until your withdrawal may still be used.

**What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions **(see contact details on the last page)**. If you remain unhappy and wish to complain formally, in England and Wales you can do this by contacting the Patient Advice and Liaison Services (PALS). In Scotland, you can contact your local hospital’s Patient Experience Team. In Northern Ireland, you can contact the Complaints Manager at your local hospital.

Contact details are: << INSERT LOCAL DETAILS HERE>>.

In the unlikely event that something does go wrong and you are harmed during the research due to someone’s negligence, then you may have grounds for legal action and compensation against the sponsor (the University of Birmingham) but you may have to pay your legal costs. The normal NHS complaints mechanisms will still be available to you, if appropriate.

**Will my details be kept confidential?**

Health and care research should serve the public interest which means that we have to demonstrate that the research serves the benefits of society as a whole. We do this by adhering to the regulations that govern clinical trials in the UK.

All information collected about you for this study will be subject to the General Data Protection Regulation and Data Protection Act 2018 for health and care research and will be kept strictly confidential. University of Birmingham is the Sponsor for this study. The University of Birmingham will be using information from your medical records in order to undertake this study and will act as the data controller. This means that the University of Birmingham are responsible for looking after your information and using it properly. University of Birmingham and the NHS will keep identifiable information about you for at least 25 years after the study has finished, to allow the results of the study to be verified if needed.

All information collected by the Sponsor will be securely stored in the CALIBRE Trial Office at the University of Birmingham, on paper and electronically and will only be accessible by authorised personnel. The only people in the University of Birmingham who will have access to information that identifies you will be people who manage the study or audit the data collection process. There is an open-access CALIBRE trial website [www.birmingham.ac.uk/calibretrial](http://www.birmingham.ac.uk/calibretrial) which contains information about the trial. No identifiable information about you will be available on this website.

The NHS will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the trial. With your permission, a copy of your signed consent form will also be sent to the University of Birmingham as sponsor for this trial.

At the CALIBRE Trial Office, you will be identified by a unique study number. In routine communication between your hospital and the CALIBRE Trial Office, you will be identified by study number, initials and date of birth*.* Data may be provided to the CALIBRE Trial Office on paper or electronically.

By taking part in the study, you will be agreeing to allow research staff from the CALIBRE Trial Office to look at the study records, including your medical records. It may be necessary to allow authorised personnel from government regulatory agencies (e.g. Medicines and Healthcare Products Regulatory Agency (MHRA), the Sponsor and/or NHS bodies to have access to your medical and research records. This is to ensure that the study is being conducted to the highest possible standards.

From time to time we may be asked to share the study information (data) we have collected with researchers running other studies in this organisation and in other organisations so that they can perform analysis on the data to answer other important questions about liver disease. These organisations may be universities, NHS organisations or companies involved in health research and may be in this country or abroad. Any such request is carefully considered by the study researchers and will only be granted if the necessary procedures and approvals are in place. This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance. Under no circumstances will you be identified in any way in any report, presentation or publication arising from this or any other study.

To allow accurate follow up of all participants it may be necessary for the CALIBRE Trial Office to contact other UK NHS bodies to provide information about your health by using your NHS number/ Community Health Index (CHI) or Health & Care number (H&C). You information will be held and maintained by central UK NHS bodies such as NHS digital.

All individuals who have access to your information have a duty of confidentiality to you.

You can withdraw your consent to our processing of your data at any time. Your rights to access change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. To safeguard your rights, we will use the minimum personally identifiable information possible. Under the provisions of the General Data Protection Regulation (GDPR) 2018, you have the right to know what information the CALIBRE Trial Office has recorded about you. If you wish to view this information, or find out more about how we use this information, please contact Legal Services at the address below. Please note that a small fee may be payable to retrieve this information.

Legal Services University of Birmingham Edgbaston Birmingham, B15 2TT

**Involvement of your family doctor**

Your GP will be kept informed of your participation in the study. By consenting to take part, you agree to us sharing your progress in the study with your GP, as needed for your clinical care.

**What will happen to any samples I give?**

Whilst blood samples will be taken these are part of your standard care and will not be used for the purposes of the trial. You will not be asked to provide more bloods samples for the trial.

**What will happen to the results of the research?**

At the end of the study, we will report results to the funder of the research and publish them in appropriate academic and professional journals and at conferences. We will contact you with the results of the study once it is finished. The publications are made available to the general public on websites such as the NIHR or PubMed, should you be interested. You will not be identified in any publication.

**Who is organising and funding the research?**

CALIBRE is funded by the National Institute for Health Research Health Technology Assessment Programme (Project Number: 16/99/02). It is sponsored by the University of Birmingham and is being organised and run on their behalf by the Birmingham Clinical Trials Unit.

No member of the research team is being paid for including you in this study.

**Who has reviewed the study?**

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the North East – York National Research Ethics Service (Reference: 18/NE/0296).

Thank you for taking the time to read this information leaflet and for considering taking part in this research study.

**If you have any questions, please contact the study research nurse on** <INSERT CONTACT DETAILS HERE>

**Alternatively, you can contact the Chief Investigator for the research study:**

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