Randomised controlled trial of
EArly transjugular intrahepatiC porTosystemic stent-shunt in
Acute Variceal Bleeding REACT-AVB trial.

RECOVERED CAPACITY: PATIENT INFORMATION SHEET

Why am I receiving this information sheet?

We are providing you with this Information Sheet because of one of the **following reasons**:

1. To inform you that you were selected to participate in a trial called REACT-AVB. You were admitted to the hospital because you have Liver Cirrhosis and were bleeding from the varices. You received the usual care treatment from the hospital clinical care team.

   The clinical care team assessed your condition and found that you were suitable to take part in the REACT-AVB trial. Because you were very unwell, consent/opinion was taken from a person who could represent you. The researcher collected most of the information needed for the trial from your medical notes, which was recorded as part of usual care by your clinical care team. This data was entered into an online database, and you were selected to one of the treatment groups randomly by a computer (you can find out more about the treatment arms further along in this PIS). You would have had a one in two chance of either treatment (like flipping a coin). Your doctors were informed of the treatment you were given. We are now seeking consent from you to **continue in the trial**.

2. It may, however, be the case that you have already provided consent to take part in the trial but during the course of the trial, you became unwell and you were unable to confirm your willingness to continue in the trial. We, therefore, contacted a person that was able to represent you and make this decision on your behalf. Now that you are well, we would like to ask you if you wish to continue in the trial and if so, ask for you to re-consent.

Can I say no?

The decision to continue to take part in this trial is entirely your own choice**. 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 Research Team members will go through the information sheet with you and answer any questions. You can talk to others about the trial if you wish. Please ask us if there is anything that is not clear.

If you do decide to **continue 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. Your consent form will stay on record in your trial file and your medical records and be available for review by the trial monitors. With your permission, a copy of your signed consent form will also be sent to the REACT-AVB Trial Office at the 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 continue to receive treatment.

Key points about this research:

- *Variceal bleeding is a serious complication of liver cirrhosis.*
- *Patients with variceal bleeding need treatment with medicines and endoscopic treatment to stop the bleeding and prevent further bleeding. This is known as standard of care (SOC).*
- *For patients at high risk of bleeding again, an "early" Transjugular Intrahepatic Portosystemic Stent-Shunt (TIPSS) is offered to reduce the risk of further bleeding.*
- *We do not know which treatment is better and this trial is being conducted to find out if early TIPSS is better than SOC.*
- *This trial will randomly assign patients to either SOC or early TIPSS.*
- *We aim to improve the care of patients with liver cirrhosis and oesophageal variceal bleeding.*

What is the purpose of the trial?

Cirrhosis (scarring of the liver) can lead to varices (abnormally enlarged veins) developing in the lower gullet (food pipe) or stomach. There's a 1 in 20 chance of varices bleeding while, 1 in 7 patients may not survive. In those who do survive, further bleeding is common. We must therefore offer the best treatment to improve survival by preventing further bleeding. We check for these varices with a device called an endoscope (a bendy tube incorporating light and a tiny video camera).

The currently accepted treatment for patients who bleed from varices is known as standard of care (SOC) and includes the following:

Endoscopic treatment

During an endoscopy procedure, using the endoscope, we can:

- Tie off an enlarged vein with a rubber ring (variceal banding) or;
- Inject a drug, with a needle, directly into the swollen vein, to cause that vein to clot which stops bleeding.

We need to do this every few weeks or months.

Medication

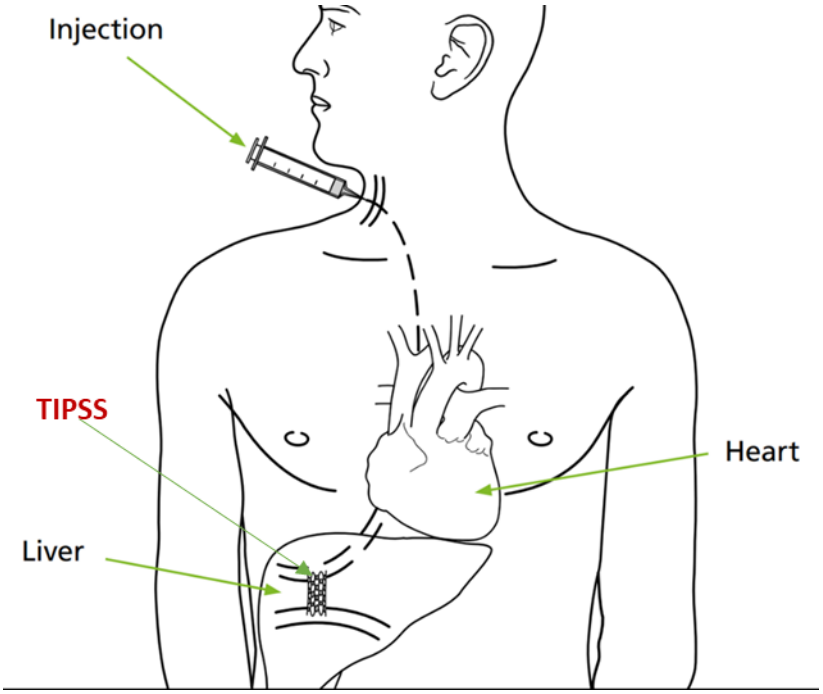
We may use antibiotics as well as other drugs. Once a patient is stable they are offered drugs called beta-blockers which slow down the heart and lower pressure in the enlarged veins, to reduce the risk of further bleeding.

TIPSS

For some patients, we use a device called a Transjugular Intrahepatic Portosystemic Stent-Shunt (TIPSS). The TIPSS procedure involves inserting a small metal tube, roughly 10mm in diameter (about the length of a grain of rice), inside the liver using a wire passed through a vein in the neck and down into the organ (through the liver). The procedure is done under sedation (so you are relaxed and sleepy) or general anaesthetic (which will put you to sleep). The procedure is done with X-ray imaging guidance.

TIPSS may be used to treat severe variceal bleeding (bleed from the varices) in:

- An emergency to stop bleeding where SOC has not worked. This is known as 'rescue' TIPSS **or;**
- Patients that are at high risk of bleeding again after satisfactory stabilisation with SOC. This is called "early" TIPSS.



Our trial on early TIPSS – the plan

There have only been a few clinical trials of early TIPSS in a small number of patients. Trial results so far have not been clear as to which patients benefit from early TIPSS or whether it is better for the patient overall. Current guidelines recommend further research. Nobody so far has compared early TIPSS with SOC in a large clinical trial and obtained clear results.

Our team has a lot of experience running clinical trials involving people with liver disease. Our team includes two patient collaborators and a Trustee of Liver4Life charity (*https://www.liver4life.org.uk/*). We will regularly involve them and other public contributors in all parts of the research.

We want to do a trial to compare early TIPSS with SOC in severe variceal bleeding to see if early TIPSS is better than SOC in improving the survival of patients. Patients will get early TIPSS or SOC at random.

The trial will seek to recruit just under 300 patients nationally over 4 years. It includes a 12-month pilot trial to address any problems early. We will also compare cost-effectiveness and quality of life for the patients for both treatments.

If we conclude that early TIPSS is more effective in terms of survival, cost, and quality of life than SOC, this could lead to a major change in clinical practice.

Are there any benefits to taking part?

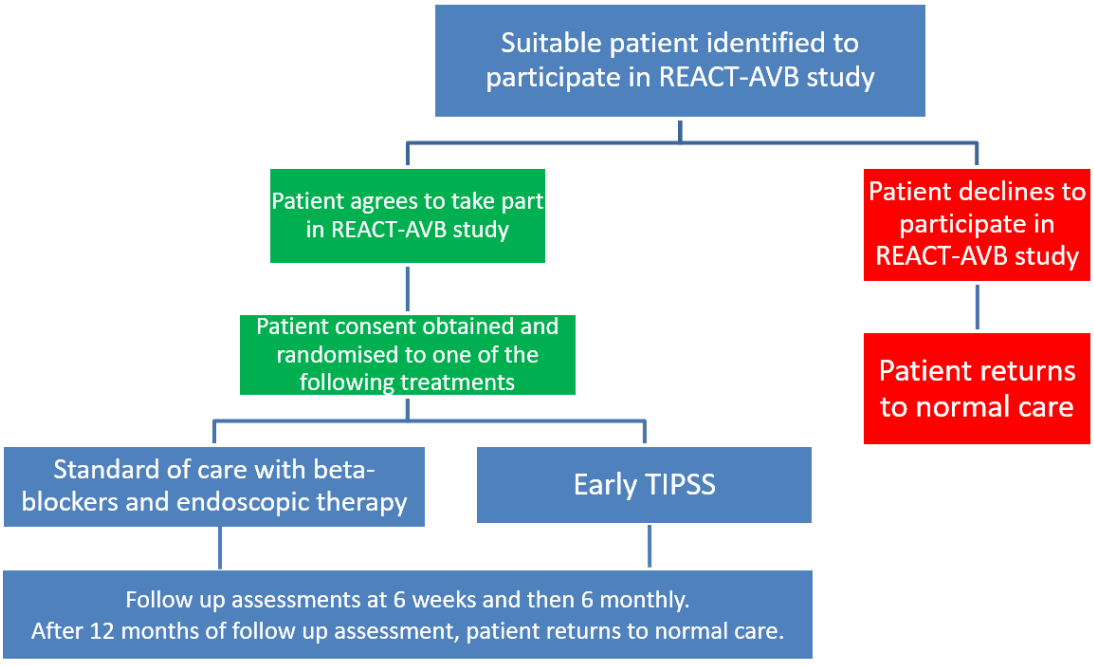
Whilst we cannot guarantee that there will be any direct benefit to you, by taking part in this trial, you may feel empowered knowing that your contribution to the results of the trial should in the future, lead to the best treatment for variceal bleeding in patients with liver cirrhosis.

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

The treatment will **continue for at least one year** (unless you decide to withdraw from the trial or any problems arise. For example, if you are randomly selected to the SOC treatment group, it may be necessary that you be considered for 'rescue' TIPSS in case you re-bleed again, as part of standard clinical care.

During the trial, at **3 separate time points, we will ask you to complete a health questionnaire form, (EQ5D-5L)**. This may be carried out face to face with the research staff or remotely over the telephone. With your permission, a copy of your form will also be sent to the REACT-AVB Trial Office.

A summary of the trial schedule is illustrated below:



During the course of the trial, you will be asked to confirm your willingness to continue in the trial. However, if your Doctor feels that you are too unwell to understand what is being asked from you then we will contact a person that would be able to make this decision on your behalf.

If you live in **Scotland**, your welfare guardian, welfare attorney or your nearest relative will be asked to provide **consent** on your behalf to continue in the trial. If you live in **England, Wales or Northern Ireland**, your partner, relative, close friend or if none of these is available, another Doctor (who is not involved in the trial) will be asked to provide their **opinion** on your behalf to continue in the trial.

Pregnancy

The TIPSS procedure and beta-blockers can harm the unborn child. **Neither pregnant women nor women who plan to become pregnant during the course of this trial should not participate in this trial**. Women who could become pregnant must use barrier contraception during the trial. If you find you have become pregnant while taking part in this trial, you should **immediately** tell a member of the research team. We will need to follow you up during your pregnancy and information about the outcome of your pregnancy will be collected from your 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 those who take part in this trial will be seen as is usual clinical practice either in the clinic or via telephone and/or/ video conference, every few months to assess their well-being. Appointments will take approximately **30 minutes**. Every patient will have an ultrasound **at 6 monthly intervals** as part of their normal care.

Patients in the **early TIPSS group** will also have an ultrasound to check that the TIPSS is working well at 2-7 days. These patients do not require further endoscopies or beta-blockers. This procedure will take approximately 30 minutes.

Patients in the **SOC group** will be prescribed regular beta-blockers and have endoscopies to treat the varices every few weeks to months depending on how well the varices respond to treatment.

Are the treatments and tests safe?

You may have had the TIPSS procedure. This would have been in addition to what you would have received if you did not take part. TIPSS has been in use for over 30 years and has few complications. During the procedure, 1 in 10 patients may experience fever or minor bleeding which normally gets better without additional treatment. Fewer than 1 in 20 patients may have more severe bleeding, infection, liver, kidney or heart failure requiring additional treatments. 1 in 3 to a half of all patients may experience confusion after/following a TIPSS. This is due to the unwanted build-up of toxic substances in the body such as ammonia, which can lead to a brain condition known as *hepatic encephalopathy*, although this normally improves with medical treatments and other measures. In previous studies, the likelihood of experiencing this was no higher with TIPSS than SOC.

The **TIPSS procedure involves exposure to x-rays**. This procedure uses ionising radiation to form images of your body and provide your doctor with other clinical information to inform treatment. Ionising radiation may cause cancer many years or decades after the exposure. We are all at risk of developing cancer in our lifetime. 50% of the population is likely to develop one of the many forms of cancer at some point in their lifetime. Taking part and being in the TIPSS arm will increase the lifetime risk of cancer by 0.18% compared to the general population.

Variceal banding has been used for over 30 years and is generally considered very safe. Around 1 in 10 patients may experience discomfort and find it difficult to tolerate. Infrequent complications may include bleeding which affects 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).

Beta-blockers were initially developed to treat high blood pressure and some forms of heart disease. As with any drug, there are potential minor side effects that affect around half of patients, but serious complications are very rare. The side effects of beta-blockers (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.

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

Do I need to worry about COVID-19?

In relation to the ongoing COVID-19 pandemic, current government guidelines and local NHS and University procedures will be followed.

What happens when the research trial stops?

After the trial finishes, your clinical care will revert to the current standard care for patients with cirrhosis and previous variceal bleeding.

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 trial. You will have the **option** to decide whether you wish to continue. A member of the Research Team may ask you to re-sign a consent form if you decide to continue. If the trial 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 trial 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 will still be used.** More information about this can be found under section; *'how will my data be kept secure?'*

What if there is a problem?

If you have a concern about any aspect of this trial, you should ask to speak to the Researcher Team 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.

The contact details are: << INSERT LOCAL DETAILS HERE>>.

In the unlikely event that something does go wrong and you are harmed during the trial 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 there be any reimbursement offered for taking part in this study?

There won't be any financial reimbursements offered for taking part in this study.

Will my details be kept confidential?

All information collected about you for this trial will be subject to the General Data Protection Regulation (GDPR) and Data Protection Act 2018 for health and care research and will be kept strictly confidential.

How we will use information about you?

The University of Birmingham is the Sponsor for this trial. They will be using information from your medical records to undertake this trial and will act as the data controller. This means that the University of Birmingham is responsible for looking after your information and using it properly. For this trial, we will collect your name, date of birth, sex, contact details, address, NHS number/Community Health Index (CHI) or Health & Care Number (H&C), ethnicity, brief demographic data, medical history and health conditions.

All information collected by the Research Team will be safely and securely stored in the REACT-AVB Trial Office at the University of Birmingham, on paper and electronically and will only be accessible by authorised personnel. People who do not need to know who you are will not be able to see your name or contact details. The only people at the University of Birmingham who will have access to information that identifies you, will be people who manage the trial or audit the data collection process. In routine communication between your hospital and the Trial Office, you will be identified by your unique trial number and partial date of birth.

By taking part in the trial, and signing the consent form you will be agreeing to allow staff from the REACT-AVB Trial Office to look at the trial records, including your medical records. It may be

necessary to allow authorised personnel from government regulatory agencies (e.g. the Sponsor and/or NHS bodies) to have access to your medical and research records. This is to ensure that the trial is being conducted to the highest possible standards.

The research team will use your name and contact details to contact you about the research trial and make sure that relevant information about the trial is recorded for your care, and 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 for this trial.

From time to time we may be asked to share the trial information (data) we have collected with researchers running other studies in this organisation and 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 maybe in this country or abroad. Any such request will be carefully considered by the trial 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 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 trial.

To allow accurate follow up of all our patients, it may be necessary for the REACT-AVB Trial Office to contact other UK NHS bodies to provide information about your health or to collect your data for other related research. This would mean that the REACT-AVB Trial Office will use some of your personal identifiers (date of birth, NHS number/ Community Health Index (CHI) or Health & Care Number (H&C), trial number, age, sex and address) to link information that these organisations hold. Your 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.

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 UK Policy Framework for Health and Social Care Research.

Where can you find out more about how your information is used?

You can find out more about how we use your information;

- At www.hra.nhs.uk/information-about-patients/
- By asking one of the Research Team
- By sending an email to the University's Data Protection Officer at dataprotection@contacts.bham.ac.uk.

There is an open-access REACT-AVB trial website www.birmingham.ac.uk/react-avb which contains information about the trial. No identifiable information about you will be available on this website.

How will my personal data be kept secure?

The University of Birmingham takes great care to ensure that personal data is handled, stored and disposed of confidentially and securely. Our staff receive regular data protection training, and the University has put in place organisational and technical measures so that personal data is processed in accordance with the data protection principles set out in data protection law.

Any physical paperwork containing identifiable data will be kept in an access-controlled and secured room inside a locked filing cabinet. In relation to this trial, electronic data will be kept on secure servers within the University of Birmingham.

When the trial is published, no identifiable or personal information will be published and so you will not be identified from it.

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 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 REACT-AVB 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

How long will my personal data be kept?

The University of Birmingham and the NHS will keep identifiable information about you for at least 10 years after the trial has finished, to allow the results of the trial to be verified if needed.
If you withdraw from the trial, **we will keep** the information we have already obtained from you but, to safeguard your rights, we will use the minimum personally-identifiable information possible.

Involvement of your family doctor.

Your GP will be kept informed of your participation in the trial. By consenting to take part, you agree to us sharing your progress in the trial 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 trial. You will **not** be asked to provide more blood samples for the trial.

What will happen to the results of the research?

At the end of the trial, we will report results to the funder of the research and publish them in appropriate academic and professional journals and at conferences. We will write our reports in a way that no-one can work out that you took part in the study. You will not be identified in any publication. The Research Team will contact you with the results of the trial once it is finished. The publications are made available to the general public on websites for the specialist societies, University of Birmingham, and NIHR should you be interested. You can also access the trial website to follow its progress and see the results when available.

Who is organising, insuring and funding the research?

REACT-AVB is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (Reference Number: 130883). 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 trial.

The University has in place Clinical Trials indemnity coverage for this trial, which provides cover for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the discretion of the University provide cover for non-negligent harm to participants.

The NHS Trust has a duty of care to its patients, in the event of clinical negligence being proven, compensation will be available via the NHS indemnity.

Who has reviewed the trial?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This trial has been reviewed and given favourable opinion by the National Research Ethics Committees (Reference: 23/WM/0085 and 23/SS/0050).

Have patients and the public been involved in this trial?

A group consisting of patients and members of the public helped to develop this research topic and the research questions that should be asked. Potential participants described the inclusion and exclusion criteria for people taking part in this trial, patient visits, and the tests.

The two patient collaborators mentioned earlier helped to develop and review this Patient Information Sheet. They will continue to be involved in the trial.

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

If you wish to seek advice about the trial from a healthcare professional who is not involved in the trial, you can contact <INSERT CONTACT DETAILS HERE> through the switchboard on the following number: <INSERT NUMBER HERE>

If you have any questions about the trial, please contact the Research Team on <INSERT CONTACT DETAILS HERE> **Alternatively, you can contact the Chief Investigator for the research trial:**

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