TRIAL PROTOCOL



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

REACT-AVB Trial

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number:	**5.0**
Version Date:	**5th August 2026**

PROTOCOL DEVELOPMENT

Protocol modifications

The following modifications and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Modifications number	Date of modifications	Protocol version number	Type of modifications	Summary of modifications
01	***10/10/2025***	***4.0***	***Substantial***	***Protocol and PI sign off sections: version and date removed and placed with blank information for CI and PI to complete going forward*** ***Sponsor contact details updated*** ***Trial Office contact details updated: additional trial social media account added*** ***Trial Management Group list: Member details updated*** ***Data Monitoring Committee list updated*** ***Trial Summary, intervention section updated with 'Early TIPSS within 5 days from 4 days'*** ***Trial Schema updated: 'Early TIPSS within 5 days from 4 days'*** ***Section 1 (1.1) updated with references to more recent meta-analysis and another early TIPPS study*** ***Section 2 (1.1) note added regarding reason for change to the TIPSS***

				window and DOI number added ***Section 5 (5.1.4) wording to include that written consent should follow telephone consent where possible*** ***Section 6 (6.3) process made more clearer regarding randomisation process*** ***Section 7 (7.1.1) Time frame for TIPSS window updated*** ***Section 7 (7.5) Time frame for TIPSS window updated*** ***Section 9 (9.1) Schedule of assessment table updated: follow up visit windows widened, 2-7 days arm assessment timepoint, full blood count, clinical examination, Doppler Ultrasound wording revised. The timepoints of when data requires to be collated also revised to align with clinical practice*** ***The accompanying text has also been updated to align with the revised table.*** ***Section 11 (11.2) Table 7 consent form wording revised*** ***Section 11 (11.3) additional wording adding to make the process for completing the EQ-5D-5L clearer*** ***Section 11 (11.5) self-evident corrections added***

				Section 11 (11.7) wording updated to make information clearer
02	***<Add date sent to REC>***	***5.0***	***Substantial***	***Protocol and PI sign off sections: version and date removed and placed with blank information for CI and PI to complete going forward*** ***Trial Management Group list: Member details updated*** ***Data Monitoring Committee list updated*** ***Trial Summary, intervention section updated with 'Early TIPSS within 7 days from 5 days'*** ***Trial Schema updated: 'Early TIPSS within 7 days from 5 days'*** ***Section 1 (1.1) updated with references to more recent meta-analysis and another early TIPPS study*** ***Section 2 (1.1) note added regarding reason for change to the TIPSS window and DOI number added*** ***Section 5 (5.1.4) wording to include that the witness needs to be an independent member of staff.*** ***Section 7 (7.1.1) Time frame for TIPSS window updated***

				Section 7 (7.1.2) Figure 1- patient pathway diagram updated ***Section 7 (7.5) Time frame for TIPSS window updated*** ***Section 9 (9.1) Schedule of Assessments table, has been updated to widen the follow-up visit window for the Week 6 assessment, aligning it more closely with routine clinical practice.*** ***Terminology updated throughout the study documentation to align with the implementation of the new Clinical Trials Regulations. References to 'amendment(s)' have been replaced with 'modification(s)', and 'trial site' has been replaced with 'trial location'.***

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PROTOCOL SIGN OFF

Chief Investigator (CI) signature page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.

Trial name:	REACT-AVB Trial
Protocol version number: Protocol version date:	Version: 5.0 05/AUG/2026
CI name:	Prof Dhiraj Tripathi
Signature and date:	_____ 22/10/2026

Sponsor statement

By signing the IRAS form for this trial, University of Birmingham, acting as sponsor, confirm approval of this protocol.

Compliance statement

This protocol describes the REACT-AVB trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the REACT-AVB trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Data Protection Act 2018, the Principles of Good Clinical Practice (GCP) and the Mental Capacity Act 2005 and subsequent modifications thereof. Every care has been taken in the drafting of this protocol, but future modifications may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise patient safety.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Trial name: Protocol version number:	REACT-AVB Trial Version: 5.0
Protocol version date:	__ __ / __ __ __ / __ __ __ __
PI name:	
Name of trial location (site):	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

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Sponsor	
University of Birmingham	
Research Strategy and Services Division Ash House University of Birmingham Edgbaston, Birmingham B15 2TT	Tel: 07814 650 003 Email: researchgovernance@contacts.bham.ac.uk

Chief Investigator	
Prof. Dhiraj Tripathi	Consultant Hepatologist and Liver Transplant Physician
Room 14, 4th Floor East, Institute of Translational Medicine Heritage Building Queen Elizabeth Hospital Mindelsohn Way Birmingham B15 2TH	Tel: 0121 371 4672 Email: dhiraj.tripathi@uhb.nhs.uk

Trial Office contact details	
Birmingham Clinical Trials Unit (BCTU) Institute of Applied Health Research College of Medical and Dental Sciences Public Health Building University of Birmingham Birmingham B15 2TT	Email: react-avb@trials.bham.ac.uk
Randomisation website	https://reactavb.bctu.bham.ac.uk/
Trial website	www.birmingham.ac.uk/react-avb
Trial social media	Twitter: www.twitter.com/avbreact Blue Sky: https://bsky.app/profile/react-avb.bsky.social

Trial Management Group	
Chief Investigator	
Prof Dhiraj Tripathi	Consultant Hepatologist and Liver Transplant Physician
Co-Chief Investigator	
Dr David Patch	Consultant Hepatologist
Co-Investigators	
Dr Homoyon Mehrzad	Consultant Interventional Radiologist
Dr Dominic Yu	Consultant Interventional Radiologist
Dr Richard Aspinall	Consultant Hepatologist
Prof Matthew Armstrong	Consultant Hepatologist
Dr Hamish Ireland	Consultant Interventional Radiologist
Dr Simon Travis	Consultant Interventional Radiologist
Prof Peter Hayes	Professor of Hepatology
Ms Mandy Lomax	PPI representative
Ms Emily Lam	PPI representative
Mrs Elizabeth Brettell	Trials Management Team Leader
Prof Susan Jowett	Reader in Health Economics
Mrs Catherine Moakes	Lead Statistician
Mrs Natalie Rowland	Methodological Lead
Miss Alisha Maher	Statistician
REACT-AVB Trial Office- Birmingham Clinical Trials Unit, University of Birmingham	
Mrs Sukhi Sehmi	Senior Trial Manager
Naomi Campton	Programming Team Lead

Trial Steering Committee	
Chair:	
Prof Graham Foster	Professor of Hepatology
Independent Members:	
Caroline Fairhurst	Senior Research Fellow Statistician
Dr Hilary White	Interventional Radiology Consultant
Mrs Helen Bold	Patient and public involvement representative
Non-Independent Members:	
Prof Dhiraj Tripathi	Consultant Hepatologist and Liver Transplant Physician
Dr David Patch	Consultant Hepatologist
Data Monitoring Committee	
Chair:	
Prof Alastair O'Brien	Independent panel member
Independent Members:	
Jonathan Moss	Honorary Professor
Dr Holly Fisher	Senior Research Associate

ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AKI	Acute Kidney Injury
BASL	British Association for the Study of Liver
BCTU	Birmingham Clinical Trials Unit
BSIR	British Society of Interventional Radiology
BSG	British Society of Gastroenterology
CI	Chief Investigator
CRF	Case Report Form
DCF	Data Clarification Form
DMC	Data Monitoring Committee
DSA	Data Sharing Agreement
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HBV-DNA	Hepatitis B Virus -Deoxyribonucleic acid
HR	Hazard Ratio
HRA	Health Research Authority
HRS	Hepatorenal Syndrome
HVPG	Hepatic Venous Pressure Gradient
ICF	Informed Consent Form
ISF	Investigator trial location (site) File
ICERs	Incremental Cost-Effectiveness Ratios
MELD	Model for End-Stage Liver Disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NSBB	Non-selective beta blocker

OR	Odds Ratio
PI	Principal Investigator
PIS	Patient Information Sheet
PSS	Personal Social Services
QALY	Quality-Adjusted Life-Year
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGT	University of Birmingham Research Governance team
RR	Relative Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TIPSS	Transjugular intrahepatic portosystemic stent-shunt
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
UoB	University of Birmingham
USS	Ultrasound scan
VBL	Variceal band ligation

TRIAL SUMMARY

Title

Randomised controlled trial of **EA**rly transjugular intrahepati**C** por**T**osystemic stent-shunt in **A**cute **V**ariceal **B**leeding (REACT-AVB).

Objectives

To investigate the clinical and cost-effectiveness of early transjugular intrahepatic portosystemic stent-shunt (TIPSS) versus endoscopic plus pharmacological therapy in patients with cirrhosis and acute variceal bleeding after initial control of bleeding by variceal band ligation (VBL).

Trial design

Pragmatic multicentre randomised controlled open label superiority two arm parallel group trial with an internal pilot.

Patient population and sample size

Patients with liver cirrhosis presenting with acute variceal bleeding which has been controlled by current therapy as recommended in the British Society of Gastroenterology (BSG) guidelines.[1]

Sample size of 294 patients (1:1 randomisation) is required to show improved transplant free survival at one year from 60% to 80% with early TIPSS with 90% power (alpha=0.05) and allowing for 20% attrition.

Setting

Acute NHS Trusts and Health Boards in the UK that admit and manage patients with acute variceal bleeding.

Eligibility criteria

Inclusion Criteria:

1. Liver cirrhosis as defined clinically, radiologically (ultrasound scan (USS) and/or transient elastography) or on histology.
2. Acute variceal bleed (oesophageal or gastric) with haemostasis following initial endoscopic therapy.
3. Child-Pugh score 7-13.
4. Age ≥ 18 years.

Exclusion Criteria:

1. Failure to control acute bleeding (as per Baveno 7 criteria)[2] prior to randomisation.
2. Previous portosystemic shunt or TIPSS.
3. Known occlusive portal vein thrombosis precluding TIPSS.
4. Active cancer including hepatocellular carcinoma affecting 1-year survival.
5. Clinically significant encephalopathy causing recurrent hospital admissions.
6. Pregnant or lactating women.
7. Evidence of heart failure refractory to treatment.
8. Severe active septicaemia refractory to treatment.

Interventions

Early transjugular intrahepatic portosystemic stent-shunt (TIPSS) within 7 days of diagnostic endoscopy.

Or;

Endoscopic therapy and non-selective beta-blocker.

Outcome measures

Primary outcome:

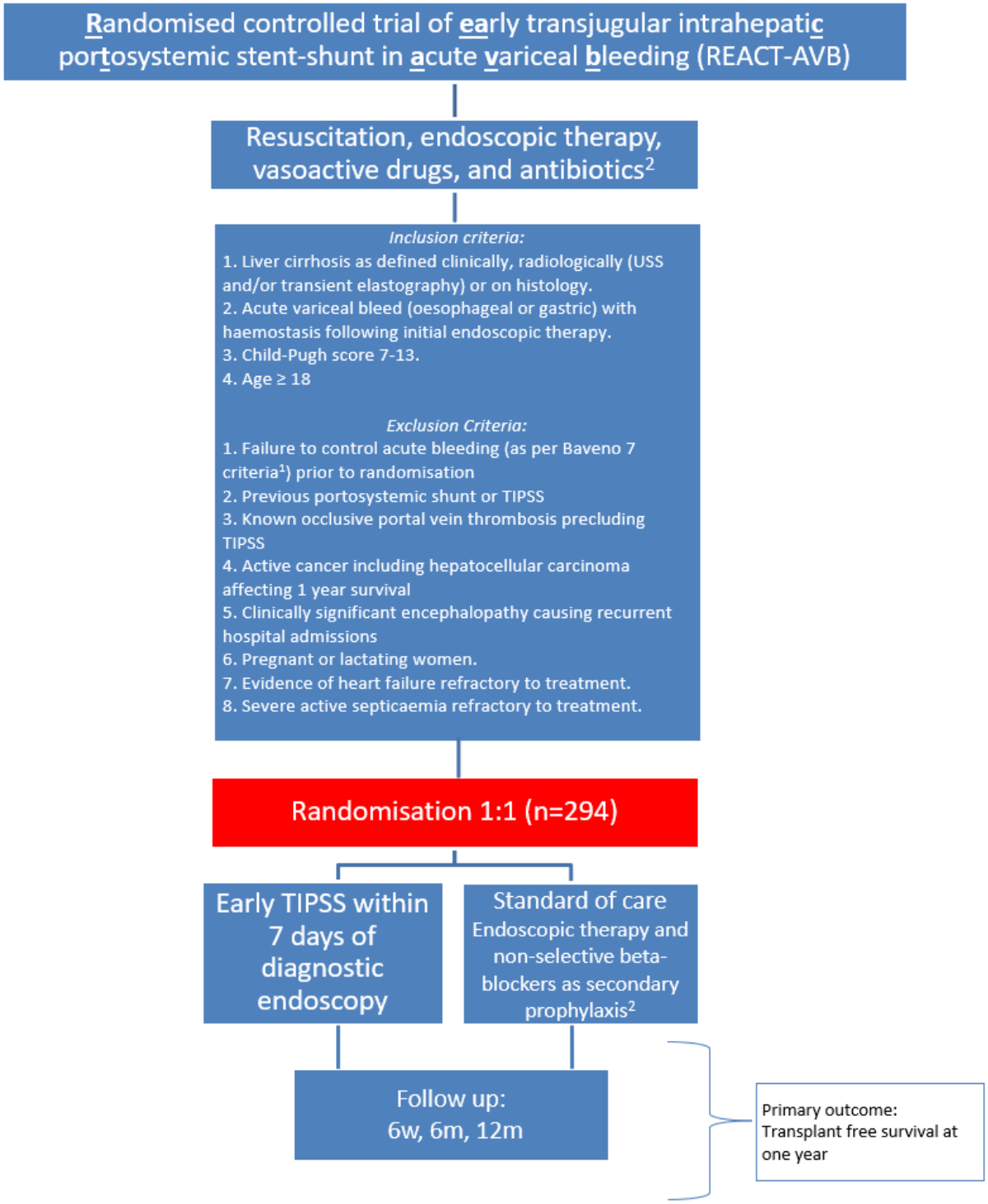
Transplant free survival at one year (post randomisation)

Secondary outcomes:

1. Transplant free survival at 6 weeks (post randomisation).
2. Rebleeding* (post randomisation):
    a. Early (less than or equal to 6 weeks)
    b. Late (greater than 6 weeks)
3. Serious adverse events related to treatment (up to 12 months post randomisation).
4. Other complications of cirrhosis (up to 12 months post randomisation):
    a. New onset ascites
    b. New onset encephalopathy
    c. Spontaneous bacterial peritonitis
    d. Hepatocellular carcinoma.
    e. Any renal dysfunction
5. Child-Pugh score at 6 and 12 months (post randomisation).
6. Model for End-Stage Liver Disease (MELD) score at 6 and 12 months (post randomisation).
7. Health-related quality of life (EQ-5D-5L) at 6 and 12 months (post randomisation).
8. Use of healthcare resources, costs and cost-effectiveness based on cost per Quality-Adjusted Life-Year (QALY) estimated using the EQ-5D-5L and cost per life year gained at one year, and modelled cost per QALY over patient lifetime.
9. Crossover therapies.

* *Rebleeding is defined as hematemesis and/or melena with either: 1) endoscopic evidence of variceal bleeding or stigmata of recent haemorrhage and at least a 2 g/L reduction in haemoglobin within 24 hours of admission; or 2) massive upper gastrointestinal bleeding leading to death. The definition includes bleeding from banding ulceration*

TRIAL SCHEMA



1. de Franchis R. J Hepatol. 2022 Apr;76(4):959-974
2. Tripathi D, *et al*. Gut. 2015;64:1680-704

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1. BACKGROUND AND RATIONALE

1.1 Background

Liver disease is the 5th largest cause of death in the United Kingdom (UK). There has been a 5-fold increase in the development of cirrhosis in 35-55-year olds between 2003-2013, with 30,000 – 60,000 at risk or affected by liver cirrhosis. A major complication of cirrhosis is portal hypertension with formation of varices. Approximately 50% of cirrhotic patients develop varices, which equates to over 25,000 prevalent cases.[3] At least 2,000 patients are admitted to hospital in England per year with variceal bleeding, which has an inpatient mortality of 15% and 1 year mortality of up to 40%.[4] Increased hospitalisation results in increased use of secondary care and substantial health care costs. Therefore, optimising the management of acute variceal bleeding to minimise the risk of variceal rebleeding and improve survival are important clinical and economic goals.

The 2015 UK guidelines from the BSG recommend endoscopic therapy (variceal band ligation (VBL) for treating acute oesophageal variceal bleeding or glue injection for acute gastric variceal bleeding) in combination with drug therapy (terlipressin and antibiotics) in acute variceal bleeding.[1, 5] Transjugular intrahepatic portosystemic stent-shunt (TIPSS) is recommended where these measures fail to control bleeding. This well-established emergency strategy is often referred to as "rescue" or "salvage" TIPSS therapy. However, although rescue TIPSS therapy controls variceal bleeding in over 90% of patients, the mortality can be as high as 36% at six weeks and 42% at 1 year.[6, 7] Patients with advanced cirrhosis (Child Pugh score >13) have high mortality and TIPSS in this patient group is likely to be futile.[6]

There has been much interest in TIPSS, not as a *rescue* therapy due to ongoing acute variceal bleeding, but as *early (i.e. prophylactic)* therapy after initial control of bleeding with endoscopic and drug therapy. The patients most likely to benefit from early TIPSS are those at highest risk of rebleeding and mortality. The risk of variceal rebleeding can be as high as 60%, with each variceal rebleeding episode associated with 20% mortality, particularly in the first five days following a bleed.[8] Therefore, early interventions during the acute variceal bleeding episode are likely to have the greatest impact on outcomes.

The concept of early TIPSS was studied in a randomised controlled trial (RCT) published in 2004. Patients with a hepatic venous pressure gradient (HVPG) >20 mmHg were randomised to early TIPSS or standard of care within 24 hours of their index variceal bleed. The trial showed higher one year mortality in the standard of care group compared with the early TIPSS group (Odds Ratio (OR) 4.25, 95% Confidence Interval (CI) 1.33 to 13.56).[9] However, use of bare stents, endoscopic sclerotherapy and pharmacological therapies at the time do not reflect current practice. Since invasive monitoring of HVPG is not available in many hospitals, clinical and biochemical parameters of liver disease severity such as the Child Pugh score[10] or the Model for End-Stage Liver Disease (MELD) score[11] have been proposed to stratify high risk patients. Garcia-Pagan *et al.* reported better 12 month transplant free survival by insertion of early polytetrafluoroethylene covered TIPSS within 72 hours of an index bleed in patients with more advanced cirrhosis (Childs C or Childs B actively bleeding) at the time of endoscopy (n=63, 86% vs. 61%, absolute risk reduction (ARR) 25%, 95% CI 2 to 48%).[12] The standard of care was banding in combination with drug therapy. A single centre RCT from China of early TIPSS (n=86, TIPSS within 72 hours of index endoscopy) versus standard of care (n=46) in Child Pugh B and C patients, reported better transplant free survival at 6 weeks and 1 year (Hazard Ratio (HR) 0·50, 95% CI 0·25 to 0·98) and improved control of bleeding or rebleeding with early TIPSS (HR 0·26, 95% CI 0·12

to 0·55).[13] The benefit was seen in all groups regardless of active bleeding. There was no difference in the incidence of hepatic encephalopathy. It is important to note that 75% of patients had chronic hepatitis B (HBV) infection (33% HBV-DNA negative). Antiviral therapy could have influenced outcomes in addition to TIPSS, and the results are difficult to extrapolate to the western populations where alcohol related liver disease predominates. Furthermore, endoscopic sclerotherapy was used in over 5% of patients, which is not in keeping with current international guidelines which recommend VBL.[1, 14]

A further RCT of early TIPSS from the UK in 58 patients with Child Pugh score ≥ 8, showed no difference in survival (HR 1.15, 95% CI 0.33 to 3.4) nor rebleeding, regardless of severity of liver disease or active bleeding.[15] It is noteworthy that the 1 year transplant free survival in the standard of care group was significantly better than in the 2010 Spanish study (76% versus 61%).[16] This would suggest improved overall care of patients with acute variceal bleeding in the last decade, therefore caution is required when extrapolating the results from the Spanish study to the present time. Furthermore, carvedilol was used in most patients in the UK study standard of care group, compared with propranolol in the Spanish study. Carvedilol has a greater effect on portal pressure,[17] and could also be a contributing factor to observed better outcomes in the UK standard of care group, although further study of carvedilol in secondary prevention of variceal bleeding is required.

The trial by Dunne *et al*. highlights the challenges in adherence to the 72-hour window for early TIPSS, with 23/29 patients (79%) actually having a TIPSS and only 13/23 receiving TIPSS within 72 hours, but all within 5 days.[15] It is however, worth noting that a previous UK RCT[18] of TIPSS versus banding for secondary prevention of variceal rebleeding, where TIPSS was placed within 72 hours of acute bleeding in all patients, had similar results to the trial by Dunne *et al.*[15] However, the standard of care was not in keeping with current practice. An important finding of all these RCTs is that rescue TIPSS was necessary in between 10% and 31% in the standard of care groups due to refractory rebleeding, and was invariably associated with very poor outcomes.

Data from observational studies has fuelled the debate regarding patient selection for early TIPSS.[19-23] While patients with Child Pugh C disease appear to have improved survival following early TIPSS, this is not always the case for Child Pugh B patients with active bleeding.[19-23] An observational study also suggested that patients with a MELD score of ≥ 19 are likely to benefit from early TIPSS, [21] a finding confirmed by Lv and colleagues.[22] It is not clear from these studies if there is a maximum threshold of severity of liver disease beyond which there is no benefit from early TIPSS.

A meta-analysis of two RCTs[9, 12] and two observational studies[24, 25] demonstrated that early TIPSS is associated with reduced overall mortality compared to standard of care (OR 0.38, 95% CI 0.17 to 0.83, P = 0.02).[19] The reduced mortality was only observed in Child C (< 14 score) patients. There was significantly less rebleeding with early TIPSS without a significant difference in hepatic encephalopathy. An individual patient data meta-analysis of 8 studies (4 RCTs[9, 12, 13, 15] and 4 observational studies[22-25]) of 1389 patients showed 1-year survival was significantly higher in the early TIPSS group than standard of care (81.6% vs. 65.4%, HR= 0.43, 95% CI: 0.32–0.60, p < 0.001).[26] The improved outcomes of early TIPSS were seen when only considering RCTs, in Child Pugh B + AB > 7 patients with active bleeding, and in Child Pugh C patients. The number of patients needed to treat to save one life was 6. There were no significant differences with respect to hepatic encephalopathy. Further analysis suggested that the benefits of pTIPSS could extend beyond 72 hours (up to one week

in Child Pugh B patients and 2 weeks in Child Pugh C patients) but this needs confirmation in RCTs. The importance of the latter was reinforced by the Baveno 8 consensus workshop in March 2026 (in press). A meta-analysis included all 4 key RCTs[9, 13, 15, 24] although it was not based on individual patient data.[27] Analysis of these RCTs demonstrated no significant difference in mortality at 6 weeks (Relative Risk (RR) 0.33, 95% CI 0.08 to 1.36) or at 1 year (RR 0.76, 95% CI 0.51 to 1.14). The authors recommended properly powered RCTs.

1.2. Trial rationale

The research question is "Does early TIPSS within 7 days of an acute variceal bleed result in improved transplant free patient survival when compared with standard of care?" The data to support universal adoption of early TIPSS in all high-risk groups is currently inadequate. An evaluation of early TIPSS with a sufficient number of patients to determine the effect on transplant free survival is a priority. Prospective study of extending the time window to 7 days is an important research agenda. Quality of life and cost effectiveness have not been well studied in previous trials, but are important outcomes to assess.

Current clinical practice guidelines produced by the British Society of Gastroenterology (BSG) recommends further research into early TIPSS with particular focus on patient selection. A document entitled "NHS England's Research Needs Assessment 2018" produced jointly by National Institute of Health and Care Research (NIHR) and National Health Service (NHS) England identified TIPSS and variceal haemorrhage as an area where some evidence exists but further research is required. [28]

1.2.1. Justification for patient population

Participants will be aged 18 years and over with liver cirrhosis presenting with acute variceal bleeding which has been controlled by current therapy as recommended in the BSG guidelines.[1] The inclusion and exclusion criteria will ensure that only patients who are likely to benefit from early TIPSS are selected. It is important to exclude patients who are unlikely to benefit from early TIPSS, and also those where TIPSS would be considered a contraindication as per the UK guidelines.

1.2.2. Justification for design

This is a pragmatic multicentre randomised controlled open-label superiority two arm parallel group trial. Patients with acute variceal bleeding will be randomised in a 1:1 ratio between TIPSS and standard of care. The controlled design ensures freedom from bias. Due to the nature of the interventions, blinding is not possible.

1.2.3. Justification for choice of intervention(s)

The aim of this study is to compare early TIPSS versus standard of care. TIPSS is currently used for acute variceal bleeding as part of standard of care in patients where endoscopic and drug therapies fail to control variceal bleeding (salvage or rescue TIPSS).[29] However, there is a lack of high-quality consistent data comparing early TIPSS with standard of care.

1.2.4. Justification of choice of primary outcome

1-year transplant free survival aligns with other trials of early TIPSS. Although TIPSS is likely to reduce rebleeding compared to standard of care, this benefit should translate to improved survival to ensure the benefits of early TIPSS outweigh the potential risks e.g. hepatic encephalopathy. The survival

benefit should take into account the competing risk of liver transplantation, hence the choice of transplant free survival.

2. AIMS AND OBJECTIVES

1.1 Internal pilot objectives

An internal pilot phase of 12 months was undertaken. The aims of the pilot phase were to assess whether the 'hub' and 'spoke' model, recruitment rate, randomisation, delivery of the intervention within the specified time and the follow-up assessment schedule were feasible. The objectives for the pilot were as follows:

- 20 trial locations (sites) (combination of 'hub' and 'spoke') to be opened during the pilot stage.
- 33 participants to be recruited across the trial locations (sites).
- >90% of the participants to receive early TIPSS within 4 calendar days of diagnostic endoscopy (intervention arm only).

The success of the internal pilot was based on the traffic light system as shown in the below Table 1 Pilot Phase Progression Criteria:

Table 1: Pilot Phase Progression Criteria

12 month pilot	Green	Amber	Red
Number of trial locations (sites) opened	>19	10-19	<10
Total number of patients recruited	>32	16-32	<16
Protocol adherence: early TIPSS within 4 calendar days of diagnostic endoscopy (intervention arm only)	>90%	80-90%	<80%

Green*: if all three criteria were green progress to the main trial.*

Amber*: if any of the criteria were amber, continuation of recruitment could be contingent on the submission (and approval) by the funder, (following consultation with the TSC), of a clear rescue plan.*

Red*: if all criteria were red seek advice from funder on continuation following consultation with the TSC.*

The trial locations (sites) primarily selected were regional TIPSS centres (referred to as **'hubs'**, i.e. those trial locations (sites) that were able to perform the early TIPSS procedure). This trial also intends to recruit from secondary care sites that **do not** perform early TIPSS but would treat emergent patients and also could provide treatment and follow-up for those patients who are randomised to the standard of care arm; these trial locations (sites) will be referred to as **'spokes'**. Where a patient is randomised at a spoke trial location (site) to the early TIPSS arm, they will be transferred to a hub trial location (site) for treatment, as per standard practice.

Protocol adherence (intervention arm only) focused in particular on:

1) Whether early TIPSS was performed.
2) Whether early TIPSS was performed within 4 days (including weekends) of diagnostic endoscopy.

Both are particularly important for spoke trial locations (sites) where transfer to a regional TIPSS centre (hub) is necessary for those randomised to the TIPSS arm.

Following the pilot phase, the protocol underwent two separate revisions to the TIPSS eligibility window. The first revision increased the window from 4 to 5 days in light of emerging evidence suggesting that early TIPSS remained beneficial within a broader timeframe (**DOI: 10.1097/HEP.0000000000000613**). Subsequently, as further evidence and international opinion indicated that TIPSS may confer benefit up to 7 days following diagnostic endoscopy, the protocol was amended again to extend the TIPSS window from 5 to 7 days.

2.1. Main trial objectives

2.1.1. Clinical aims and objectives

The primary clinical objective is to investigate whether early TIPSS improves transplant free survival at one year compared to endoscopic plus pharmacological therapy in patients with cirrhosis and acute variceal bleeding after initial control of bleeding by VBL.

The Secondary objectives are to assess:

1) Rebleeding rates less than or equal to 6 weeks from randomisation and post 6 weeks to a year.
2) Complications of cirrhosis as outlined in the secondary outcomes.
3) Severity of the patient's liver disease (MELD and Child Pugh scores) at baseline, 6 and 12 months post randomisation.
4) Patient's quality of life (EQ-5D-5L) at baseline, 6 and 12 months post randomisation.
5) Safety of TIPSS vs. endoscopic plus pharmacological therapy up to 12 months post randomisation.

2.1.2. Economic aims and objectives

The economics objectives are to investigate the use of healthcare resources, costs and cost-effectiveness based on cost per Quality-Adjusted Life-Year (QALY) estimated using the EQ-5D-5L and cost per life year gained at one year, and modelled cost per QALY over patient lifetime.

3. TRIAL DESIGN AND SETTING

3.1. Trial design

REACT-AVB is a pragmatic multicentre randomised controlled open-label two arm superiority parallel group trial with an internal pilot.

3.2. Trial setting

Acute NHS Trusts and Health Boards in the UK that admit and manage patients with acute variceal bleeding.

3.3. Assessment of risk

All clinical trials can be considered to involve an element of risk and in accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures, this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care.

REACT-AVB is a non-CTIMP that has been formally risk assessed by BCTU as 'low risk with no higher than the risk of usual care in this setting' on the basis that both the intervention and control arms are already in common usage throughout the UK and the safety profiles are well established.

A Risk Assessment has been conducted documenting the risks associated with the trial and corresponding mitigation. The Risk Assessment will be subject to review throughout the lifetime of the trial.

4. ELIGIBILITY

4.1. Inclusion criteria

1) Liver cirrhosis as defined clinically, radiologically (USS and/or transient elastography) or on histology.
2) Acute variceal bleed (oesophageal or gastric) with haemostasis following initial endoscopic therapy.
3) Child-Pugh score 7-13.
4) Age ≥ 18 years.

4.2. Exclusion criteria

1) Failure to control acute bleeding (as per Baveno 7 criteria)[2] prior to randomisation.
2) Previous portosystemic shunt or TIPSS.
3) Known occlusive portal vein thrombosis precluding TIPSS.
4) Active cancer including hepatocellular carcinoma affecting 1 year survival.
5) Clinically significant encephalopathy causing recurrent hospital admissions.
6) Pregnant or lactating women.
7) Evidence of heart failure refractory to treatment.
8) Severe active septicaemia refractory to treatment.

4.3. Co-enrolment

Due to the emergency nature of this trial, the research team at the trial location (site) is highly unlikely to be aware if a patient is already participating in a clinical trial. Where a patient is subsequently found to have been participating in a concurrent trial, the trial location (site) should inform the REACT-AVB Trial Office, who will in turn request that the Chief Investigator (CI; or delegate) assess whether there may be any safety concerns or impact on the trial data. Any such concerns would be communicated to the trial location (site) and the CI of the other trial and appropriate remedial action taken as necessary. The trial location (site) should follow their local procedure for reporting trial co-enrolment to the sponsor of BOTH trials

Where appropriate, once in the REACT-AVB trial, participants may take part in any other observational study. Co-enrolment in other trials will be considered on a case-by-case basis, after discussion with the Trial Management Group (TMG). The trial location (site) should contact the REACT-AVB Trial Office should any such queries arise.

5. CONSENT

Patients or their legal representative/ consultee will be approached initially by a member of the clinical team delivering their standard care. With the patient's/ legal representative's/ consultee's agreement, a member of the research team will approach them to provide further information about the trial.

Patients who present with acute variceal bleeding, will by default, be critically ill due to the effects of blood loss, sedation, possible infection and possible delirium, and therefore may lack capacity to consent for themselves. Trial locations (sites) should follow the appropriate consent procedure depending on the patient's mental status. Where the potential patient lacks capacity to consent for themselves, advice will be sought from a consultee (for trial locations (sites) in England, Wales and Northern Ireland; see section 5.1.2) or consent will be sought from a legal representative (for trial locations (sites) in Scotland; see section 5.1.3).

The Principal Investigator (PI) is responsible for obtaining written informed consent for each patient and/or advice from a consultee or consent from a legal representative, prior to performing any trial related procedures. This can also be taken by other members of staff at the trial location (site) (e.g. Research Nurse) if local practice allows and this responsibility has been delegated by the PI and is documented on the Site Signature and Delegation Log.

5.1 Consent Procedure

5.1.1 Patients with capacity to give written consent

A Patient Information Sheet (PIS) will be provided to facilitate the process of consent. To avoid overwhelming patients who are already facing a life-threatening condition, a Summary PIS will be provided. Unless the full PIS is requested during the consent process, it will be provided later when the patient's condition is felt to have stabilised. The PI or delegate will ensure that they adequately explain the aims of the trial, the trial interventions, anticipated benefits, and potential hazards of taking part in the trial. They will also explain that participation in the trial is voluntary and they can refuse to take part and may withdraw from the trial at any time without this affecting their care.

The patient will be given sufficient time to read the PIS, have the opportunity to ask questions and, if desired, discuss their participation with others beyond the clinical or research team. If the patient expresses an interest in participating in the trial, they will be asked to sign and date the latest version of the Informed Consent Form (ICF). The consent will document that the patient understands and acknowledges that a copy of the signed ICF will be transferred to the REACT-AVB Trial Office for review. In situations where the patient has capacity and has agreed to join the trial, but is unable to physically sign the ICF (e.g. unable to hold a pen), a witness will countersign the ICF (the witness MUST NOT be on the Site Signature and Delegation Log).

The PI or delegate will countersign and date the ICF. A copy of the ICF will be given to the patient, filed in the medical notes, sent to the REACT-AVB Trial Office and the original placed in the Investigator trial location (site) File (ISF). Once the patient is entered into the trial, the patient's trial number will be entered on the ICF and maintained in the ISF.

5.1.2 Patients lacking capacity to give consent (**for** trial locations (sites) **in England and Wales**)

The PI or delegate should seek advice from a consultee on whether the patient would wish to be included in the trial. A consultee is not asked to give consent on behalf of the potential participant, but rather to provide an opinion on the views and feelings of the potential patient. They will be given sufficient time to read the Consultee Information Sheet and have the opportunity to ask questions and discuss the trial with others beyond the clinical or research team.

A personal consultee is an individual who cares for the adult lacking capacity, or is interested in that individual's welfare, but is not doing so for remuneration or acting in a professional capacity. If a personal consultee is not available or unwilling to give advice, then a nominated consultee, i.e. a professional who is independent of the REACT-AVB trial, can do so.

The consultee must be informed that they are:

- Being asked to advise on the views and feelings they believe the patient would have towards participating in the REACT-AVB Trial.
- Free to decide whether they would like to provide this advice.

The consultee will be provided with sufficient understandable information about the REACT-AVB Trial so that they can provide informed advice.

The advice given by consultees will be recorded on a Consultee Declaration Form. A copy of the form will be given to the consultee, filed in the medical notes, sent to the REACT-AVB Trial Office for review and the original placed in the Investigator trial location (site) File (ISF). If/when the patient regains capacity during the study, the PI or delegate will follow the procedure in Section 5.1.5 and confirm on-going consent.

5.1.3 Patients lacking capacity to give consent (for trial locations (sites) in Scotland)

The PI or delegate should ask a legal representative to provide consent on behalf of an adult who lacks capacity to do so themselves. Those who are able to act as a legal representative include the patient's welfare guardian or welfare attorney, and if one is not appointed, the patient's nearest relative.

The legal representative must be informed that they are:

- Being asked to give consent on behalf of the incapacitated patient.
- Free to decide whether they wish to make this decision or not.
- Being asked to consider what the patient would want, and to set aside their own personal views when making this decision.

The legal representative will be provided with sufficient understandable information, in an understandable form, about the REACT-AVB Trial to ensure that they can make an informed decision. They will be given sufficient time to read the Legal Representative Information Sheet and have the opportunity to ask questions and discuss the trial with others beyond the clinical or research team.

The consent given by the legal representative will be recorded on a Legal Representative Consent Form. A copy of the form will be given to the legal representative, filed in the medical notes, sent to the REACT-AVB Trial Office for review and the original placed in the Investigator trial location (site) File (ISF). If/when the patient regains capacity during the study, the PI or delegate will follow the procedure in section 5.1.5 and confirm on-going consent.

5.1.4 Remote consent (consultees and legal representatives)

If a consultee/ legal representative is not available in person, but the trial location (site) has access to their contact details (e.g. in the case of a personal representative, they are listed as a next of kin), then once the clinical team at the trial location (site) has informed the consultee/ legal representative of the patient's condition and sought their agreement to be approached about the study, the research team will approach them to seek their advice/ consent remotely (either by telephone or video call). The researcher at the trial location (site) will discuss the study with the consultee/ legal representative in the presence of a witness. The researcher will sign and date the ICF with a witness present (the

witness needs to be an independent member of staff). The witness will also be asked to sign and date the ICF. The verbal consent discussion will be documented in the patient's medical record and the patient will be enrolled into the study. A copy of the PIS and signed ICF will be provided to the participant and consultee/legal representative as soon as possible. As above, the original will be placed in the ISF, a copy sent to the REACT-AVB Trial Office and a copy placed in the participant's medical notes. Written consent should be obtained from the participant further to telephone consent, where possible.

5.1.5 When patient regains capacity

In all cases within the UK, where the patient regains capacity, the research team at the trial location (site) will seek consent from them, at the earliest opportunity. The participant will be provided with the current ethically approved **Recovered Capacity PIS** and **Recovered** ICF form. The processes outlined in section 5.1.1 should be followed. The consultee or legal representative should be informed of this at the outset. Should the patient express a view that they no longer wish to take part in the REACT-AVB trial; their opinion will supersede that of the consultee or legal representative.

5.2 Consent documentation

Details of the informed consent discussions with the patient, consultee or legal representative will be recorded in the patient's medical notes. This will include date of discussion, name of the trial, summary of discussion, version number of the documents given to the patient/consultee/legal representative, and date consent/advice received. Where consent/advice is obtained on the same day that the trial specific procedures are due to start, a note should be made in the medical notes as to what time the consent/advice was obtained, and procedures started.

5.3 On-going consent

At each visit, the participant's willingness to continue in the trial will be ascertained (through the participant, consultee, or legal representative as appropriate) and documented in the medical notes.

If the participant does not have the capacity at any of the visits, then the PI or delegate will need to seek advice from a consultee or consent from a legal representative whether the participant continues and complete the ICF. The procedures outlined in section 5.1.2 or 5.1.3 will need to be followed and documented in the medical notes.

If/when the patient regains capacity again, the PI or delegate will follow the procedure in section 5.1.5 and confirm on-going consent.

Throughout the trial, the participant, consultee or legal representative will have the opportunity to ask questions about the trial.

Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the decision to continue, the participant, consultee or legal representative will be given time to consider this information and if happy to continue they will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

5.4 Consent for linkage to routine health data

There is an additional statement in the ICFs for the participant/consultee/legal representative to acknowledge that they understand that the REACT-AVB Trial Office might in the future, to allow for accurate follow-up or for other related research, collect patient data available in NHS routine clinical datasets, including primary care data (e.g., Clinical Practice Research Datalink, The Health Improvement Network, QResearch) and secondary care data (Hospital Episode Statistics) through NHS

Digital and other central UK NHS bodies. The participant/consultee/legal representative will acknowledge that they understand that the Trial Office might send the patient's name, address, date of birth, sex, NHS number (CHI number, Scotland; H&C number, Northern Ireland) and trial number, to the relevant national registry, and then for the national registry to link this to their data and send the information back to the Trial Office. The acknowledgement by the participant/consultee/legal representative will also allow access to other new central UK NHS databases that will appear in the future. This will allow the REACT-AVB Trial Office (subject to receipt of additional funding via another grant application) to assess longer-term impact and health service usage data without needing further contact with the participants.

6. ENROLMENT, RANDOMISATION and BLINDING

6.1. Identification

The research will take place in acute NHS hospitals with provision for management of variceal bleeding in the secondary and tertiary care setting. Patients will be recruited from at least 30 hospitals offering a 24-hour service for patients admitted with acute variceal bleeding.

6.1.1 Identification of trial location (site) – hub and spoke model.

Hub: Regional TIPSS centres will be considered 'hub' trial locations (sites) and will be able to randomise participants to either arm and perform either treatment intervention. Hubs will also be expected to accept participants randomised from 'spoke' trial location (sites) who have been allocated to the TIPSS intervention.

The spoke will need to ensure that arrangements are in place to enable the timely transfer of TIPSS participants to the hubs to perform treatment.

Spoke: Trial locations (sites) that do not routinely perform TIPSS but routinely refer (as per standard clinical practice) patients for TIPSS procedures will be referred to as spokes. Prior to activating spokes, the REACT-AVB Trial Office will ensure that a regional hub has been activated.

6.1.2 Identification of patients

Patients will be identified by the clinical team through regular screening of patients admitted with variceal bleeding and emergency endoscopy procedures for gastrointestinal bleeding. Where patients are randomised in trial location (site) not offering TIPSS, those randomised to early TIPSS will be transferred to regional centres (hubs) and those randomised to standard of care will be managed as per routine practice, usually at the spoke site where they were first admitted.

For logistical reasons, outside of the trial location's (site) control, some participants who have been randomised to the TIPSS arm may not be able to receive the intervention (e.g. due to unanticipated resource issues at the trial location (site) or an inability to conduct the procedure due to the patient's health status). If this occurs, it will be documented on the follow-up case report form (CRF).

All participants will receive standard of care for initial control of bleeding consisting of resuscitation, endoscopic therapy within 24 hours of admission with variceal bleed, vasoactive drugs, and antibiotics. (Figure 1).[1]

Standard of care arm: Participants in this group will receive secondary prophylaxis with endoscopic therapy (as per BSG guidelines[1]) in combination with non-selective beta blocker (NSBB).

Early TIPSS arm: TIPSS will be performed within 7 days of a diagnostic endoscopy that confirms variceal bleeding.

Details of all patients approached about the trial will be recorded on the REACT-AVB Patient Screening/Enrolment Log which will be kept in the ISF and should be available to be sent to the Trial Office upon request.

6.2. Randomisation

Randomisation will be provided by BCTU using a secure online system (available at https://reactavb.bctu.bham.ac.uk/), thereby ensuring allocation concealment. Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising patients into the trial as detailed on the REACT-AVB Site Signature and Delegation Log. These unique log-in details must not be shared with other staff and in no circumstances should staff at the trial locations (sites) access either system using another person's login details. The online system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

In the event of the online system not being available, a back-up telephone toll-free randomisation service (0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays, government guided closures and University of Birmingham closed days.

6.3. Randomisation process

After eligibility for randomisation has been confirmed and informed consent/advice from a consultee has been given, the patient can be randomised into the trial using the online system. A paper CRF replicating the completed electronic Randomisation Form should also be completed and a copy should be returned to the REACT-AVB Trial Office. All questions and data items on the online Randomisation Form must be answered prior to a potential patient being randomised into the trial and a Trial Number being issued.

Following randomisation, a confirmatory e-mail will be sent to the PI and other members of the research team.

The local research team should add the participant to the REACT-AVB Participant Recruitment and Identification Log, which links participants with their Trial Number. PIs must maintain this document securely and it must not be submitted to the REACT-AVB Trial Office. The REACT-AVB Participant Recruitment and Identification Log should be held in strict confidence.

6.3.1. Randomisation method

Participants with acute variceal bleeding will be randomised at the level of the individual, in a 1:1 ratio between early TIPSS and standard of care. A minimisation algorithm will be used within the online randomisation system to ensure balance in the intervention allocations over the following variables:

- Childs-Pugh score (7-9, 10-13)
- Intubation for endoscopy (yes/no)
- Antibiotics administered (yes/no) (prior to diagnostic endoscopy or no more than 24h afterwards).
- Terlipressin administered (yes/no) (before or no more than 24h after diagnostic endoscopy).
- Active bleeding* at point of diagnostic endoscopy (yes/no).
- Recruiting centre.

**bleeding from the varices at time of endoscopy including stigmata bleeding.*

To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.4. Blinding

Due to the two interventions in the trial being so different, it is not feasible to have a blinded design. Furthermore, there are treatment implications for the patients following their allocated procedure, and therefore the research staff need to be aware of the intervention received.

The primary outcome is objective (transplant-free survival at 12 months), thus minimising the risk of bias.

6.5. Informing the patient's GP and other parties

If the participant/legal representative/consultee has agreed, the participant's GP should be notified that they are in the REACT-AVB trial, using the REACT-AVB GP Letter.

7. TRIAL INTERVENTION

7.1. Trial intervention(s)

7.1.1. TIPSS

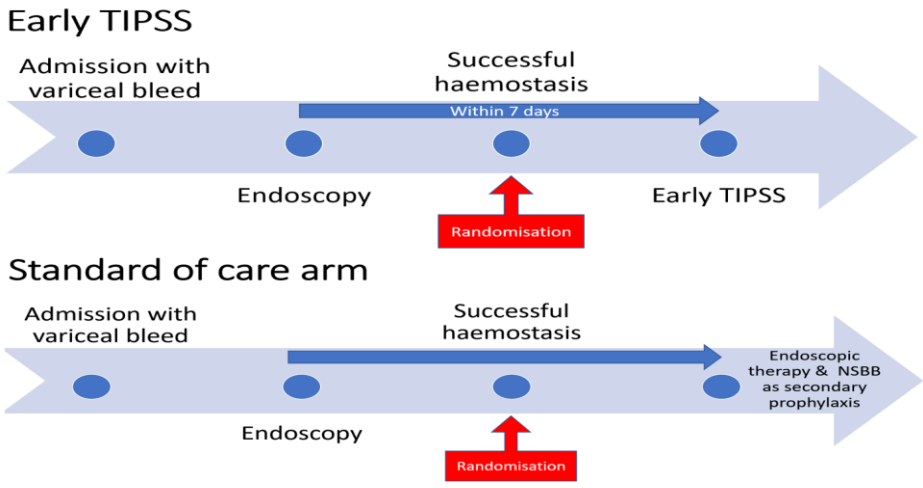
TIPSS is a procedure used in routine practice and should be undertaken in accordance with any applicable local policies and care pathways, ideally adhering to BSG guidance.29 The procedure is done under fluoroscopic guidance with use of x-rays. Early TIPSS is delivered as per standard clinical practice and no trial specific mandates on administration apply. This includes any standard modifications as described in 7.2. The time frame for early TIPSS is within 7 days of diagnostic endoscopy.

It is the operator's choice to decide whether general anaesthesia or deep sedation is most appropriate.

7.1.2. Standard care arm

Participants will undergo secondary prophylaxis against variceal rebleeding which usually comprises a combination of VBL and NSBB as per the BSG guidelines.[1]

Figure 1: Patient pathways



7.2. Intervention modification or discontinuation

In the TIPSS arm, modification (in line with local practice) may be needed in the following situations:

1. TIPSS occlusion
2. Refractory hepatic encephalopathy requiring reduction in the size of the stent or occlusion of stent
3. If participant has a liver transplant, then TIPSS will be removed at the time of surgery

In the standard of care arm, modification (in line with local practice) may be needed in the following situation:

1. Participant may be intolerant of banding or NSBB which could lead to discontinuation of treatment
2. Participant may choose to stop NSBB or banding
3. Serious Adverse Events (SAE) related to banding or NSBB e.g. allergic reaction or banding induced stricture or bleeding
4. If participant has a liver transplant banding and NSBB are discontinued

7.3. Continuation of intervention after the trial

Both treatments are currently in use in normal clinical practice and therefore the participant will continue to be treated after the trial has ended as per the standard care pathway.

7.4. Accountability

Medications used as standard to treat variceal bleeding will be taken from standard hospital pharmacy stock. As REACT-AVB does not fall under the Medicines for Human Use (Clinical Trials) regulations 2004, segregated stocks for trial use and specific trial labelling is not required. Temperature monitoring should follow local pharmacy practice and deviations need not be reported to the REACT-AVB Trial Office. The shunt is regularly used in TIPSS procedure and hence this is not classed as a device study. Therefore the study does not fall under medical devices regulations.

7.5. Adherence

TIPSS arm: Adherence to TIPSS will be defined as a participant receiving their TIPSS surgery within 7 days of diagnostic endoscopy. If TIPSS is not performed or is performed outside the specified time window, the reasons for this will be captured on a REACT-AVB CRF.

Standard of care arm: Adherence to standard care will be defined as a participant not receiving TIPSS for any indication. If participants in the standard of care arm do receive TIPSS, the reasons for this will be captured on a REACT-AVB CRF.

8. OUTCOME MEASURES

8.1. Main trial outcomes

8.1.1. Primary outcome

1. Transplant free survival at one year post randomisation

8.1.2. Secondary outcomes

8.2.2.1 Clinical

1. Transplant free survival at 6 weeks (post randomisation)
2. Rebleeding* (post randomisation):
    a. Early (less than or equal to 6 weeks)
    b. Late (greater than 6 weeks)
3. Serious adverse events related to treatment (up to 12 months post randomisation)
4. Other complications of cirrhosis (up to 12 months post randomisation):
    a. New onset ascites
    b. New onset encephalopathy
    c. Spontaneous bacterial peritonitis
    d. Hepatocellular carcinoma
    e. Any renal dysfunction
5. Child-Pugh score at 6 and 12 months post randomisation
6. MELD score at 6 and 12 months post randomisation
7. Crossover therapies

* Rebleeding is defined *as hematemesis and/or melena with either: 1) endoscopic evidence of variceal bleeding or stigmata of recent haemorrhage and at least a 2 g/L reduction in haemoglobin within 24 hours of admission; or 2) massive upper gastrointestinal bleeding leading to death. The definition includes bleeding from banding ulceration*

8.2.2.2 Economic

1. Health-related quality of life (EQ-5D-5L) at 6 and 12 months post randomisation
2. Use of healthcare resources, costs and cost-effectiveness based on cost per Quality-Adjusted Life-Year (QALY) estimated using the EQ-5D-5L and cost per life year gained at one year, and modelled cost per QALY over patient lifetime.

9. TRIAL PROCEDURES

9.1. Schedule of Assessments

Table 2: Schedule of Assessments

Assessment	Eligibility and randomisation	Baseline	Discharge Form	6 weeks ±21 days	Month 6 ±28 days	Month 12 ±28 days
Inclusion criteria*	x					
Exclusion criteria*	x					
Seek informed consent	x					
Relevant medical history taken	x					
Concomitant medication		x		x	x	x
Randomisation	x					
Bloods as per Baseline CRF)		x				
TIPSS procedure under fluoroscopic guidance**		x				
Renal function				x	x	x
Clotting profile	x			x	x	x
Liver function	x			x	x	x
Diagnostic Endoscopy	x					
Targeted clinical examination		x		x	x	x
Liver Imaging ****	x				x	x
Safety reporting		x	x	x	x	x
Quality of life questionnaires (EQ-5D-5L)		x			x	x
Child Pugh Score ***	x				x	x
MELD Score		x			x	x

refer to section 4 inclusion and exclusion criteria.

****early TIPSS arm only***

***** Child Pugh Score is a minimisation variable.***

****** this could be USS or other imaging modality***

Eligibility and Randomisation:

Eligibility will be checked (as per section 4) and consent will be obtained, prior to randomisation and participant receiving the allocated intervention.

Baseline: Participant's details of clinical examination and blood results will be taken from their medical notes as defined in the CRF. Refer to **Table 2.**

The site research team will start to monitor and record any adverse events and serious adverse events as described in section 10.3.

Discharge Form:

The Discharge Form will be applicable for all participants.

If the doppler ultrasound is performed to check TIPSS patency then this will be captured on the Discharge Form. Reporting of SAEs will also be captured on this form.

Follow up visits at 6 weeks, 6 and 12 months:

These will take place during the participants' standard outpatient visits and routine data will be collected and recorded on the CRF. The 6-week visit could be conducted as a telephone consultation if the patient is unable to attend a face-to-face clinic appointment. The 6- and 12-month times points require an in-person appointment for full clinical assessment. Further details are noted in **Table 2**.

9.2. Withdrawal and changes in levels of participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation at all visits. Participants should be aware from the beginning that they can freely withdraw (cease to participate) from the trial at any time. A participant may wish to cease to participate in a *particular* aspect of the trial.

Participants found to be ineligible post-randomisation should be followed up according to all trial processes and will still have their data analysed unless they explicitly change their level of participation.

The changes in levels of participation within the trial are categorised in the following ways:

No trial intervention: The participant would no longer like to receive the trial intervention but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e., the participant has agreed that data can be collected and used in the trial analysis).

No trial related follow-up: The participant does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e., the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).

No further data collection: The participant is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e., only data collected prior to any changes of levels in participation can be used in the trial analysis).

The details of changes of levels in participation within trial (date, reason and category of status change) should be clearly documented in the source documents.

10. ADVERSE EVENT REPORTING

10.1.Definitions

Table 3: Adverse event reporting definitions

Severity Definitions	Mild	Awareness of signs or symptoms that do not interfere with the patient's usual activity or are transient and resolved without treatment and with no sequelae.
	Moderate	A sign or symptom, which interferes with the patient's usual activity.
	Severe	Incapacity with inability to do work or perform usual activities.
Adverse Event	AE	Any untoward medical occurrence in a patient participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event	RE	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Consists of a congenital anomaly/ birth defect Or is otherwise considered medically significant by the Investigator**
Unexpected Event	UE	The type of event that is not listed in the protocol as an expected occurrence.
Related and Unexpected Serious Adverse Event	N/A	A SAE that meets both the definition of a Related and Unexpected Event.

** The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.*

*** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definitions above.*

10.2.Adverse event recording – general

The recording and reporting of Adverse Events (AEs) will be in accordance with the Principles of Good Clinical Practice (GCP) as defined by the UK Policy Framework for Health and Social Care Research and the requirements of the Health Research Authority (HRA). Definitions for adverse event reporting are listed in Table 3 in Section 10.1.

It is routine practice to record AEs in the patient's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also of causality (relatedness) in relation to the intervention(s) in accordance with the protocol.

10.3.Adverse event reporting in REACT-AVB

The safety profile for this trial population and interventions are well characterised so a strategy of targeted reporting of AEs will be employed and this will not affect the safety of participants.

Only those AEs that meet the definition of 'serious' (Table 3) will be reported as outlined below.

The reporting period for **SAEs** in REACT-AVB will be from the day of randomisation until the end of trial follow-up.

10.4.Serious Adverse Advents (SAE) reporting in REACT-AVB

For all SAEs, the PI or delegate must do one of the following:

1. **Record safety reporting-exempt SAEs** in the medical notes but **not report** them to the REACT-AVB Trial Office on a SAE Form as per Section 10.4.1 Serious Adverse Events not requiring reporting to the REACT-AVB Trial Office.

2. **Report SAEs to the REACT-AVB Trial Office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per Section 10.4.2 Serious Adverse Events requiring **non-expedited** reporting to the REACT-AVB Trial Office.

3. **Report SAEs to the REACT-AVB Trial Office in an expedited manner** (within 24 hours of the site research team becoming aware of the event). The only SAE that should be reported in this manner is death. Where a participant dies, this must be reported as per Section 10.5 SAE Reporting process.

10.4.1. Serious Adverse Events not requiring reporting to the REACT-AVB Trial Office

The only events that require reporting to the REACT-AVB Trial Office are defined in Sections 10.4.2 and 10.4.3.

Any other events that meet the definition of serious must be recorded in the patient notes, including the causality and severity, throughout the participant's time in the trial, including follow-up.

10.4.2. Serious Adverse Events requiring **non-expedited** reporting to the REACT-AVB Trial Office

Where the safety profile is well established, the causal relationship between the intervention (or the patient's underlying condition), and the SAE, may be known. That is, such events are protocol-defined as **"expected"** (see Section 10.5.2 Assessment of expectedness of an SAE by the CI).

Such events should still be recorded by the research team in the patient's notes and reported to the Trial Office on the REACT-AVB follow-up CRFs **but do not require expedited reporting** since the assessment of expectedness for the specified events has been pre-defined. These include:

All participants (see Appendix 1-5)

- Hepatic encephalopathy
- Ascites
- Hepatocellular carcinoma
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome (HRS) type of acute kidney injury (AKI)

Participants who have received the TIPSS procedure

- Haemoperitoneum
- Biliary peritonitis
- Hepatic infarction
- Trauma to hepatic artery or branches
- Renal failure
- Liver failure
- Heart failure
- TIPSS infection

Participants who have received standard of care

Participants who have had variceal band ligation:

- Banding-related bleeding

Participants who have had NSBBs:

- Heart failure
- Syncope

10.4.3. Serious Adverse Events requiring **expedited reporting** to the REACT-AVB Trial Office

The only SAE that should be reported in an expedited manner to the REACT-AVB Trial Office is participant death. Participant death should be reported on a trial specific SAE form within 24 hours of the site research team becoming aware of the event. There is an exception to this – the unlikely event that a female participant becomes pregnant whilst in the trial. In this instance, where any of the SAEs described in Section 10.8 occur during the participant's pregnancy, they too should be reported to the REACT-AVB Trial Office in an expedited manner.

10.5. SAE Reporting process

On becoming aware that a patient has experienced a SAE which requires reporting, the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the REACT-AVB Trial Office.

To report a SAE to the REACT-AVB Trial Office, the PI or delegate must complete, date and sign the appropriate trial specific CRF. Depending on whether the event is subjected to **expedited** reporting or not, this will be either a Follow-up CRF or SAE Form (Sections 10.4.2 and 10.4.3).

Where an event is reported using a SAE Form, the completed form together with any other relevant, appropriately anonymised, data should be submitted to the REACT-AVB Trial Office using the information below in accordance with the timeline given in Section10.4.3.

To report an SAE, submit the SAE Form to: react-avb@trials.bham.ac.uk

Where a SAE Form has been completed by someone other than the PI initially, the original SAE Form must be countersigned by the PI to confirm agreement with the causality and severity assessments.

Upon receipt of an SAE Form, the REACT-AVB Trial Office will allocate a unique reference number to the SAE and notify the trial location (site) by email as confirmation of receipt. The trial location (site) and the REACT-AVB Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the ISF.

If the trial location (site) has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE identification number within 1 working day of reporting, the trial location (site) should contact the REACT-AVB Trial Office.

10.5.1. Assessment of causality *(for SAEs requiring expedited reporting)*

When completing the SAE form, the PI (or medically qualified delegate) will be asked to define the nature of the seriousness and causality (relatedness; see **Table 4**) of the event.

In defining the causality, the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per **Table 4**, all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the REACT-AVB Trial Office as 'related'; all events considered at the trial location (site) to be 'unlikely' or 'unrelated' to the intervention will be reported by the REACT-AVB Trial Office as 'unrelated'. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

Table 4: Categories of causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the patient's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

On receipt of a SAE Form, the REACT-AVB Trial Office will forward it, with the unique reference number, to the CI or delegate, who will independently* review the causality of the SAE. A SAE judged by the PI or CI or delegate to have a reasonable causal relationship ("Related" as per **Table 4**) with the intervention will be regarded as a related SAE. The severity and causality assessment given by the PI will not be downgraded by the CI or delegate. If the CI or delegate disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

**Where the CI is also the reporting PI an independent clinical causality review will be performed.*

10.5.2. Assessment of expectedness of an SAE by the CI *(for SAEs requiring expedited reporting)*

The CI or delegate will also assess all related SAEs for expectedness with reference to the criteria in **Table 5**.

Table 5: Categories of expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the relevant safety information. For the REACT-AVB trial, the reference safety information will be Section 10.4.2 of the approved REACT-AVB protocol.
Unexpected	An adverse event that is <u>not</u> consistent with known information about the trial related procedures.

If the event is unexpected (i.e., it is not defined in the protocol as an expected event) it will be classified as a related and unexpected SAE.

The CI will undertake review of all SAEs and may request further information from the clinical team at the trial location (site) for any given event(s) to assist in this.

10.5.3. Provision of SAE follow-up information *(for SAEs requiring expedited reporting)*

Following reporting of a SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the REACT-AVB Trial Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, a copy of the final version of the completed SAE form must be submitted to the REACT-AVB Trial Office and the original kept in the ISF.

10.6. Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

The REACT-AVB Trial Office will submit a progress report to the Research Ethics Committee (REC) and University of Birmingham (UoB) Research Governance Team (RGT) annually starting 12 months after the date of the favourable opinion was given. An electronic copy should be emailed to the REC within 30 days of the end of the reporting period.

The REACT-AVB Trial Office will report all events categorised as Unexpected and Related SAEs to the REC and RGT within 15 days of being notified.

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to the PIs. A copy of any such correspondence should be filed in the ISF and Trial Master File (TMF).

10.7. Urgent Safety Measures

If any urgent safety measures are taken, the REACT-AVB Trial Office shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the reason why they have been taken.

10.8. Follow up of pregnancy outcomes for potential SAEs

Known pregnancy at the time of randomisation is an exclusion criterion; however, in the unlikely event that a participant becomes pregnant during the course of the trial, this will need to be reported using the trial-specific Pregnancy Notification Form. This form will also capture pregnancy outcomes. Where the following outcomes are reported, they will also be defined as a SAE and should be reported according to the process described in Section 10.4.3:

- Induced abortion (**medical reason**)
- Miscarriage
- Stillbirth
- Birth defect(s)
- Neonatal unit admission
- Neonatal death

There are no identified risks to children, born to fathers who have received any of the trial treatments. As such where the partner of a father who is participating in the trial becomes pregnant, the REACT-AVB Trial Office does not need to be notified.

11. DATA HANDLING AND RECORD KEEPING

11.1.Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained.

The source data will be classed as where the data was **first** recorded. Some data variables may be entered directly onto the CRF, these are clearly identified and detailed in the table below (see **Table 6:** Source data in the REACT-AVB trial). In situations where trial locations (sites) do not enter directly onto the CRF, relevant entries into participants' medical notes that are generated and maintained at the trial location (site) will be regarded as source data. The EQ-5D-5L Forms will be completed at the trial location (site) and filed into the participant's medical notes. Copies of the completed CRFs and EQ-5D-5L Forms will be sent to the REACT-AVB Trial Office where they will be entered onto the database.

Table 6: Source data in the REACT-AVB trial.

Data	Source
Patient Reported Outcomes (EQ-5D-5L)	These are obtained by interview directly with the participant for transcription onto the database. The original participant-completed form is the source.
Lab results	The original lab report (which may be electronic) is the source and will be kept and maintained, in line with normal local practice. Information will be transcribed onto the database.
Imaging	An interpretation of the imaging will be provided onto the CRF. Where data are interpreted, or document onto which it is transcribed, becomes the source.
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper patient records. Clinical events reported by the participant, either in or out of clinic (e.g., phone calls), must be documented in the source documents.
Health economics (resource use) data	Data will be entered on the database following interview with the participant and/ or from transcription from the source data.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.
Withdrawal	Where a patient expresses a wish to withdraw, the conversation must be documented in the source documents.

11.2. Case Report Form (CRF) completion

For the REACT-AVB trial, CRFs will be paper records completed at the trial location (site), only by those staff delegated the task of doing so. The REACT-AVB site training log and REACT-AVB Delegation Log will identify all those personnel with responsibilities for data collection.

Where possible, outcome data will be extracted from participant's medical notes and laboratory reports, to complete the REACT-AVB trial paper CRFs (see **Table 7:** CRFs for REACT-AVB).

A CRF is required and should be completed for each individual participant. The data held on the completed original CRFs are the sole property of the respective PIs whilst the data set as a whole is the property of the Sponsor and should not be made available in any form to third parties except for authorised representatives or appropriate regulatory authorities without written permission from the Sponsor.

The CRFs will include (but will NOT be limited to) the following Forms (see Table 7: CRFs).

Table 7: CRFs for REACT-AVB

Form Name	**Schedule for submission**
Consent Forms or equivalent	Copy sent to the REACT-AVB Trial Office following patient consent
Randomisation Form	At the point of randomisation
Baseline Form	As soon as possible following randomisation
Discharge Form	As soon as possible after the participant is discharged from their initial admission
Follow-up Form including patient reported outcome measures	As soon as possible after each follow-up assessment time point
Serious Adverse Event Form	If expedited: provided within 24 hours of the trial location (site) research team becoming aware of event If non-expedited: SAEs should be collected on the follow up CRFs at the scheduled time points
Pregnancy Notification Form	As soon as possible after becoming aware of participant's pregnancy
Change of Status Form	As soon as possible after the point of reduced participation or death

Forms will be considered "complete" once all data fields have been either completed unambiguously or it has been made explicit that the data is unobtainable. On completion, the original or copy of each form will be submitted to BCTU and a true copy filed in the Investigator Site File.

In all cases it remains the responsibility of the trial location's (site) PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the trial location's (site) PI, or delegate(s), on the CRF.

The delegated staff entering the data should ensure the accuracy, completeness and timeliness of the data reported.

The following guidance applies to data and partial data:

- Only CRFs provided by the REACT-AVB Trial Office should be used.
- Date format and partial dates – all dates should be in the format of DD/MMM/YYYY
- Original completed ICF should be filed in the ISF and a copy sent to the REACT-AVB Trial Office.
- Entries made on the SAE form and ICF should be made in dark ink and must be legible.
- Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated.
- Time format – all times should be in accordance with the 24hr clock
- Rounding conventions – rounding should be to the nearest whole number: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. **Example**: 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. **Example**: 3.4 rounded to the nearest whole number is 3
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible
- Missing/incomplete data – should be clearly indicated – all blank fields will be queried by the Trial Office
- Repeat laboratory tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.
- Protocol and GCP non-compliances should be reported to the Trial Office on discovery.

11.3. Patient completed questionnaires

The EQ-5D-5L will be completed at baseline, 6 and 12 months.

Participants will be asked to complete the questionnaire with staff in clinic or over the telephone. The questions will be read to the participant verbatim and responses must not be led by the person assisting with the form completion. Participants should be encouraged to respond to all questions but can decline to answer any of the questions should they wish.

On completion, of the **EQ5D-5L** a copy or a scan of the form will be sent to the Trial Office and the original filed in the participant's notes.

11.4.Data management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan and include the processes of data entry, data queries and self-evident corrections on trial data.

Data entry will be completed by the REACT-AVB Trial Office staff via a bespoke BCTU trial database. The system will include data validations to improve data quality (e.g. to prevent nonsensical dates or numerical values). Changes to the data, on the system, will be made by REACT-AVB Trial Office staff and will be documented and attributable. Trial location (site) staff will not have access to alter CRF data on the online database but will be given a 'read-only view' of the database.

Missing and ambiguous data will be queried using a data clarification system in line with the REACT-AVB Data Management Plan, and will focus on data required for trial outcome analysis and safety reporting. Queries will be raised using data clarification forms (DCFs) via the trial database, with the expectation that these queries will be completed by the trial location (site) within 30 days of receipt. Overdue data entry and data queries will be requested on a monthly basis.

11.5.Self-evident corrections

The following self-evident corrections will be allowed for data entered on behalf of the trial locations (sites) at BCTU:

- Dates: amendment of incorrect year (where the error is obvious) for forms completed at the start of a new year to allow online data entry.
- Dates: Amendment of date format to allow online data entry (e.g. DDMMYYYY instead of DDMMMYYYY as specified on CRF)
- Spelling: Correction of general spelling mistakes with reference to an English dictionary.
- Trial number: Where the trial number is incorrectly recorded on the paper CRF, but the patient can be unequivocally identified from the other patient identifiers on the form, the number may be amended to allow online data entry.

Self-Evident corrections will only be made to non-critical data items and will be agreed with the PI prior to implementation.

11.6.Data security

UoB has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act 2018 and subsequent modifications). The REACT-AVB Trial Office has arrangements in place for the secure storage and processing of the trial data, which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fireproof safe.

Logical measures for access control and privilege management: including restricted accessibility, access-controlled servers, and separate controls of non-identifiable data.

Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.

System management: the system will be developed by the Programming Team at the Trial Office, and will be implemented and maintained by the Programming Team.

System design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role-based security controls.

Operational processes: the data will be processed and stored within BCTU.

System audit: The system will benefit from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic IT risk assessment

Data Protection Registration: UoB's Data Protection Registration number is Z6195856.

11.7.Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g., signed ICFs, Investigator Site Files, Pharmacy Files, patients' hospital notes,) at their trial location (site) are securely retained for the contractual period. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU Director or their delegate.

The TMF will be stored at BCTU for at least 3 years after the end of the trial. Long-term off site data archiving facilities will be considered for storage after this time. All data will be stored securely and confidentially for at least 10 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1.Trial location (site) set-up and initiation

All PIs will be asked to sign the necessary agreements including a Site Signature and Delegation log between the PI and the REACT-AVB Trial Office and supply a current CV and GCP certificate. All members of the trial location (site) research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI. The Site Signature and Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform the Trial Office of any changes in the trial location (site) research team.

Prior to commencing recruitment, each recruiting trial location (site) will undergo a process of site initiation, either a meeting or a tele/videoconference, at which key members of the trial location (site) research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Trial locations (sites) will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

12.2.Monitoring

The central and trial location on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

12.2.1. Trial location on-site monitoring

For this trial, all trial locations (sites) will be monitored in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the REACT-AVB Trial Office and any issues noted will be followed up to resolution. Additional trial location on-site monitoring visits may

be triggered. PIs and site research teams will allow the REACT-AVB Trial Office access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff.

12.2.2. Central monitoring

The REACT-AVB Trial Office will check received ICFs and the data entered by the trial location (site) for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the Data Management Plan. The trial location (site) will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

12.3. Audit and inspection

The PI will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their trial location (site) and provide direct access to source data/documents. The investigator will comply with these visits and any required follow-up. Trial locations (sites) are also requested to notify the REACT-AVB Trial Office of any relevant inspections or local audits.

12.4. Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial. Trial locations (sites) are therefore requested to notify the REACT-AVB Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether or not a serious breach has occurred, trial locations (sites) are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Trial locations (sites) may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

13. END OF TRIAL DEFINITION

The end of trial will be 6 months from the date of the last data capture including resolution of DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. The Trial Office will notify the REC and the Sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the REC within 15 days of the end of trial. The Trial Office will provide the REC and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

14. STATISTICAL CONSIDERATIONS

14.1 Sample size

The meta-analysis by Delentre showed that early TIPSS results in an over 60% reduction in mortality compared with standard of care.[19] However, we believe this is an overestimate when considering recent RCTs, and propose a more conservative estimate. [13, 15] We have based our sample size on being able to detect a difference in transplant-free survival between two arms (standard care vs. TIPSS) using a two-sided log-rank test. We have assumed a 1 year transplant free survival rate in the standard care group of 60% and 80% in the TIPSS group (HR 0.44). To detect this difference with 90% power (alpha=0.05), and allowing for 20% attrition, we require 294 participants (147 per arm).

14.2 Analysis of outcomes

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of the planned analyses is given below.

The primary comparison groups will be composed of those randomised to standard of care versus those randomised to TIPSS. In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the intervention group to which they were randomised irrespective of adherence to randomised intervention or protocol deviations. For all outcomes, appropriate summary statistics and differences between groups will be presented, with 95% confidence intervals. Where possible intervention effects will be adjusted for the minimisation variables listed in Section 6, Enrolment Randomisation and Blinding. No adjustment for multiple comparisons will be made.

14.2.1. Primary outcome(s)

The primary outcome will be compared between treatment arms using survival analysis methods. A Cox proportional hazard model will be fitted if the assumptions of proportionality are met, and an adjusted hazards ratio with a 95% confidence interval will be presented. The p-value relating to the intervention group parameter as generated by the model will be presented. Kaplan-Meier survival curves will be constructed for visual presentation.

14.2.2. Secondary outcomes

Secondary outcomes which are considered time to event outcomes (transplant free survival at 6 weeks) will be analysed in the same manner as the primary outcome (with the exception of p-value reporting). Secondary outcomes which are considered binary (e.g. rebleeding, complications of cirrhosis and use of crossover therapies) will be summarised using frequencies and percentages. A log binomial regression model will be fitted and results presented as adjusted risk ratios, risk differences and 95% confidence intervals. Continuous outcomes (CHILD Pugh and MELD scores) will be reported using means and standard deviations at each time point. A mixed-effects repeated measures model will be fitted and results presented as mean differences and 95% confidence intervals at the primary time points (6 and 12 months). Longitudinal plots of the mean scores over time by treatment group will be produced for visual inspection of the data.

14.2.3. Planned subgroup analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see Section 6, Enrolment Randomisation and Blinding) and performed on the primary outcome only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the regression model, which will be presented alongside the effect estimate and 95% confidence interval within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

14.2.4. Missing data and sensitivity analyses

Every attempt will be made to collect full follow-up data on all participants; it is thus anticipated that missing data will be minimal. Any participants with missing primary outcome data up to 12 months will be included in the primary analysis up to the point where their clinical status (mortality and transplant data) is last known (censored at this point), and therefore no sensitivity analyses to assess

the impact of missing data are proposed for the primary outcome. Full details of any other sensitivity analyses will be included in the Statistical Analysis Plan.

14.3.Planned final analyses

The primary analysis for the trial will occur once all participants have completed the 12-month follow-up assessment and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis.

15. HEALTH ECONOMICS

The economic evaluation will assess the cost-effectiveness of early TIPSS vs standard of care by calculating the cost per life year gained and cost per QALY gained over 12 months and lifetime from an NHS and Personal Social Services (PSS) perspective. Initially, a within-trial cost-effectiveness analysis will be conducted based on the outcomes of cost per life year gained and cost per QALY estimated using the EQ-5D-5L. Decision modelling will then be undertaken to extrapolate beyond the results of the trial and assess the effect of these interventions on the longer-term outcomes such as liver failure, liver transplant and death.

15.1.Within-trial economic evaluation

Prevention of liver transplantation and death is the primary outcome of the clinical trial, and therefore it is important to evaluate the cost-effectiveness of early TIPSS based on the mortality component of this outcome. The use of QALYs as an outcome allows the comparison of the results across different diseases and interventions using a common threshold value for cost per QALY. Participants will be given the EQ-5D-5L to complete at baseline, 6 and 12 months. Participants who are unconscious and unable to complete the baseline EQ-5D-5L will be assigned the utility score for 'unconscious'. Responses will be converted to utility scores using the crosswalk algorithm as recommended by National; Institute for Health and Care Excellence (NICE) unless guidance on the most appropriate value set is updated before analysis is undertaken. Resource use information will be prospectively collected at regular follow-up hospital appointments and entered onto the database. Resources include costs of the intervention (early TIPSS) and standard of care (endoscopic treatment, medications), rebleeding, liver failure and transplantation, any follow-up care including outpatient visits, investigations (e.g. endoscopy), inpatient stays, admission to intensive care unit, treatment of adverse events and other complications, readmissions, and primary, community and social care contacts. Unit cost data will be obtained from standard national sources and other secondary sources where appropriate.

Mean costs and outcomes will be estimated for both trial arms and non-parametric bootstrapping will be used to estimate 95% confidence intervals around differences in mean costs, EQ-5D scores and QALYs. In the base case, where there is missing cost and outcome data, multiple imputation will be used. EQ-5D-5L scores will be used to generate QALYs using the area under the curve approach. Imbalances in baseline utility (EQ-5D-5L scores) between trial arms will be controlled for using a regression approach. Incremental cost-effectiveness ratios (ICERs) will then be calculated. Cost-effectiveness acceptability curves will be used to plot the probability of each intervention being cost-effective at different thresholds of willingness to pay per additional unit of outcome.]

15.2.Model-based economic evaluation

If there is evidence from the trial that differences between Early TIPSS and standard of care exist in terms of liver transplantation and mortality as well as other outcomes that may have significant cost or outcome implications beyond the trial period, a model-based economic evaluation will also be conducted. A Markov-model is the most appropriate model type, due to the lifetime time horizon, potential progression of disease, long term implications of liver transplantation and recurrence of events. The model structure will be informed by reviewing previous modelling studies and also consulting clinical experts within the team.

To parameterise the model, we will utilise clinical and economic evidence collected as part of the trial and other secondary sources. The cost-utility (cost per QALY) analysis will be conducted from the NHS/PSS perspective, using a lifetime horizon and discount rates of 3.5% for costs and outcomes. Deterministic and probabilistic sensitivity analyses will be conducted to explore the robustness of the results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results. Cost-effectiveness acceptability curves will be used to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. Value of information analysis will also be undertaken to investigate the value of, and the need for, further information on key uncertain model parameters. All methods and analyses will be reported as recommended by the CHEERS reporting guidelines.[30]

16. SUB-STUDY

There are no sub-studies within this trial.

17. TRIAL ORGANISATIONAL STRUCTURE

17.1. Sponsor

The Sponsor for this trial is University of Birmingham (UoB).

17.2. Coordinating centre

The trial coordinating centre is Birmingham Clinical Trials Unit (BCTU), based at UoB.

17.3. Trial Management Group

The Trial Management Group comprises individuals responsible for the day-to-day management of the trial: the CI, Co-Investigators (clinical and non-clinical), PPI, Health Economist, Statisticians, Trial Team Leader, Trial Manager and Data Manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet sufficiently frequently to fulfil its function.

17.4. Trial Steering Committee

A Trial Steering Committee (TSC), comprising independent and non-independent members, will be established for the REACT-AVB trial and will meet as required depending on the needs of the trial. Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the role of the TSC is to provide oversight of the trial. The TSC will monitor trial progress and conduct, and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the

recommendations of the Data Monitoring Committee (DMC). The TSC will operate in accordance with a trial specific TSC Charter.

17.5. Data Monitoring Committee

The role of the independent DMC is to monitor the trial data, and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and (where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence.

The DMC will operate in accordance with a trial specific DMC Charter which will define the membership, roles and responsibilities of the DMC. The DMC will meet at least annually as a minimum. Additional meetings may be called if needed e.g., recruitment is faster than anticipated or a safety issue is identified.

17.6. Finance

The research costs of the trial are funded by the National Institute for Health and Care Research (NIHR) Health Technologies Assessment (HTA) Programme (NIHR Ref: 130883), awarded to Prof. Dhiraj Tripathi of the UoB. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess intervention costs associated with the trial, e.g., gaining consent, are estimated in the Statement of Activities. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

18. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the principles of GCP as defined by the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent modifications), which include Data Protection Act 2018, the Mental Capacity Act 2005. The protocol will be submitted to and approved by the REC prior to the start of the trial.

Before any patients are enrolled into the trial, the PI at each trial location (site) is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent modifications gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

19. DATA PROTECTION AND CONFIDENTIALITY

Personal data and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent modifications). Personal data categories that will be collected and analysed include *name, date of birth, sex, health information, medical history,* NHS Number (**Only for England & Wales**), CHI Number (**Only for Scotland**) and H&C Number (**Only for Northern Ireland**) and address.

Participants will only be identified by their unique trial identification number *and partial date of birth* on CRFs and on any correspondence with the Trial Office. Participant/legal representative or consultee will acknowledge the transfer and storage of their informed consent form to the REACT-AVB Trial Office. This will be used to perform central monitoring of the consent process. Participants will acknowledge the transfer of their personal data for the purpose of medical research to the REACT-AVB Trial Office who will be processing data on behalf of the trial.

In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records. Representatives of the REACT-AVB trial team and sponsor may be required to have access to participants' notes for quality assurance purposes, but they should be reassured that their confidentiality will be respected at all times. The REACT-AVB Trial Office will maintain the confidentiality of all participant data and will not disclose information by which they may be identified to any third party.

20. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

21. INSURANCE AND INDEMNITY

UoB has in place clinical trials indemnity coverage for this trial which provides cover to UoB 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 UoB's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at the trial location (site) and other clinical care of the patient, responsibility for the care of the participant remains with the NHS organisation responsible for the clinical trial location (site) and is therefore indemnified through the NHS Litigation Authority.

22. POST-TRIAL CARE

When the participant has completed follow-up or if they withdraw fully from the REACT-AVB Trial they will follow their normal usual care pathway.

23. ACCESS TO FINAL DATASET

The final dataset will be available to members of the TMG and co-applicant group who need access to the data to undertake the final analyses.

Requests for data generated during this study will be considered by BCTU. Data will typically be available 6 months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is

subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified research groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: The Trial Sponsor, the relevant Trial Management Group (TMG), and independent TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of patient identifiable information. Any data transfer will use a secure and encrypted method.

24. PUBLICATION PLAN

Outputs from this trial will be submitted for publication in peer reviewed journals and the findings of the trial will be made public. Manuscripts will be prepared by the writing group as defined in the trial publication plan. Manuscripts should be submitted to the TMG in a timely fashion and in advance of being submitted for publication to allow time for review.

In all publications, authors should acknowledge that the trial was performed with the support of NIHR HTA and BCTU. Intellectual property rights will be addressed in the Clinical Study Trial location (site) Agreement between Sponsor and the trial location (site).

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26.Appendix 1

International Club of Ascites (ICA-AKI) new definitions for the diagnosis and management of AKI in patients with cirrhosis.[31]

Subject	Definition		
Baseline sCr	A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used In patients without a previous sCr value, the sCr on admission should be used as baseline		
Definition of AKI	Increase in sCr ≥0.3 mg/dL (≥26.5 µmol/L) within 48 h; or a percentage increase sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days		
Staging of AKI	Stage 1: increase in sCr ≥0.3 mg/dL (26.5 µmol/L) or an increase in sCr ≥1.5-fold to twofold from baseline Stage 2: increase in sCr >two to threefold from baseline Stage 3: increase of sCr >threefold from baseline or sCr ≥4.0 mg/dL (353.6 µmol/L) with an acute increase ≥0.3 mg/dL (26.5 µmol/L) or initiation of renal replacement therapy		
Progression of AKI	Progression		Regression
	Progression of AKI to a higher stage and/or need for RRT		Regression of AKI to a lower stage
Response to treatment	No response	Partial response	Full response
	No regression of AKI	Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dL (26.5 µmol/L) above the baseline value	Return of sCr to a value within 0.3 mg/dL (26.5 µmol/L) of the baseline value

- **AKI, acute kidney injury; RRT, renal replacement therapy; sCr, serum creatinine.**

27.Appendix 2

Diagnostic criteria of hepatorenal syndrome (HRS) type of acute kidney injury (AKI) in patients with cirrhosis.[31]

HRS-AKI

- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI according to ICA-AKI criteria
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g/kg bodyweight
- Absence of shock
- No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc)
- No macroscopic signs of structural kidney injury*, defined as:
    - absence of proteinuria (>500 mg/day)
    - absence of microhaematuria (>50 RBCs per high power field)
    - normal findings on renal ultrasonography

**Patients who fulfil these criteria may still have structural damage such as tubular damage. Urine biomarkers will become an important element in making a more accurate differential diagnosis between HRS and acute tubular necrosis.*

ICA, International Club of Ascites; NSAIDs, non-steroidal anti-inflammatory drugs; RBCs, red blood cells.

28.Appendix 3

International Club of Ascites grading of ascites.[32]

Uncomplicated ascites:

Grade 1 (mild)	Ascites is only detectable by ultrasound examination.
Grade 2 (moderate)	Ascites causing moderate symmetrical distension of the abdomen.
Grade 3 (large)	Ascites causing marked abdominal distension.

Refractory ascites:

Diuretic resistant ascites	Ascites that is refractory to dietary sodium restriction and intensive diuretic treatment (spironolactone 400 mg/day and frusemide 160 mg/day for at least one week, and a salt restricted diet of less than 90 mmol/day (5.2 g of salt)/day).
Diuretic intractable ascites	Ascites that is refractory to therapy due to the development of diuretic induced complications that preclude the use of an effective diuretic dosage.

29.Appendix 4

West-Haven Criteria for Hepatic Encephalopathy (HE).[33]

Stage	Consciousness	Intellect and Behaviour	Neurologic Findings
0	Normal	Normal	Normal examination; if impaired psychomotor testing, consider minimal hepatic encephalopathy
1	Mild lack of awareness	Shortened attention span	Impaired addition or subtraction; mild asterixis or tremor
2	Lethargic	Disoriented; Inappropriate behaviour	Obvious asterixis; Slurred speech
3	Somnolent but arousable	Gross disorientation; Bizarre behaviour	Muscular rigidity and clonus; Hyperreflexia
4	Coma	Coma	Decerebrate posturing

30.Appendix 5

BCLC classification of hepatocellular carcinoma.[34]

- *Stage 0: The tumour is less than 2 cm, the person feels well (performance status 0) and the liver is working normally*
- *Stage A: There is a single tumour less than 5 cm, or up to 3 tumours all less than 3cm. The person feels well and is active (performance status 0) and the liver is working well*
- *Stage B: There are many tumours in the liver, but the person feels well (performance status 0) and the liver is working well*
- *Stage C: The cancer has spread into the blood vessels, lymph nodes or other body organs. Or the person does not feel well (performance status 1 or 2). The liver is still working.*
- *Stage D: There is severe liver damage or the person is not well and needs help in being looked after (performance status 3 or 4)*