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

CALIBRE

PROTOCOL

Version 1.0, 1st August 2018

This protocol has regard for the HRA guidance and is compliant with SPIRIT

Sponsor:	**University of Birmingham**
Chief Investigator:	**Dr. Dhiraj Tripathi**
Coordinating Centre:	**Birmingham Clinical Trials Unit**
Funder:	**National Institute for Health Research (NIHR) Health and Technologies Assessment (HTA) Programme**
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ISRCTN:	**73887615**
REC Ref. No.:	**18/NE/0296**
Sponsor's Ref. No.:	**RG_17-229**

PROTOCOL DEVELOPMENT

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

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment

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PROTOCOL SIGN OFF

CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.

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 study publically 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 planned in this protocol will be explained.

This protocol has been approved by:

Trial Name:	Carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE)
Protocol Version Number:	Version: 1.0
Protocol Version Date:	01 / 08 / 2018
CI Name:	Dr. Dhiraj Tripathi
Trial Role:	Chief Investigator
Signature and date:	 19 / 10 / 2018

Sponsor statement:

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

Reference Numbers	
EudraCT number	2018-002488-24
Sponsor number	RG_17-229
ISRCTN reference number	73887615
IRAS reference number	248487

PI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.

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.

This protocol has been approved by:

Trial Name:	Carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE)
Protocol Version Number:	Version: 1.0
Protocol Version Date:	01 / 08 / 2018
PI Name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BCTU	Birmingham Clinical Trials Unit at the University of Birmingham
BNF	British National Formulary
BSG	British Society of Gastroenterology
CAPA	Corrective and Preventative Action
CI	Chief Investigator
CRF	Case Report Form
CRPD	Clinical Practice Research Datalink
CTA	Clinical Trial Authorisation
DIBD	Developmental International Birth Date
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
EQ-5D-5L	EuroQol Group 5 Dimensional- 5 Level questionnaire
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episode Statistics
ICA	International Club of Ascites
ICA-AKI	International Club of Ascites – Acute Kidney Injury
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MHRA	Medicines and Healthcare Products Regulatory Authority
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NIHR	National Institute for Health Research
NSBBs	Non-Selective Beta-Blockers
ONS	Office of National Statistics
PI	Principal Investigator – the local lead investigator for the **CALIBRE** Trial

PIS	Participant Information Sheet
PT	Prothrombin Time
QALY	Quality-adjusted Life-year
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
U&Es	Urea and Electrolytes
USS	Ultrasound Scan
VBL	Variceal Band Ligation

DEFINITIONS

Term	Abbreviation	Description
Birmingham Clinical Trials Unit	BCTU	The co-ordinating centre for the **CALIBRE** Trial.
Policies	POL	Policies are developed to describe the approach of the University of Birmingham (UoB) on areas that heavily regulated. Policies may also be developed when there is ambiguity in how regulatory requirements should be implemented in the Quality Management System (QMS) or when procedures to be captured in the QMS address areas controversial within the UoB at the time of implementation. Policies explain why the UoB has its procedures, especially when they seem to deviate from the regulatory requirements. Policies should be read in conjunction with the relevant SOP. Policies that are not part of a Quality Manual are coded up as 'POL'.
Quality Control Documents	QCD	Quality Control Documents can be instructions, forms, templates or checklists. They are developed to share best practices, promote standardisation to guarantee quality standards are maintained and reduce resources otherwise needed to develop similar documents. Unless indicated otherwise in the relevant Standard Operating Procedure (SOP), QCDs are not mandatory and are designed to be an optional aid to UoB staff.
Quality Management System	QMS	A Quality Management System (QMS) is a system that includes procedures and policies to describe how certain tasks should be performed and that encapsulate any standards and/or regulatory requirements that may apply to those tasks. By adhering to the Quality Management System, the user and the UoB will be assured that applicable regulations are adhered to.
Source Data		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.
Standard Operating Procedures	SOP	Standard Operating Procedures are detailed written instructions to achieve uniformity in the performance of a specific function. They define tasks, allocate responsibilities, detail processes, indicate documents and templates to be used and cross-reference to other work instructions and guidance or policy documents. They are standards to which the UoB may be audited or inspected.

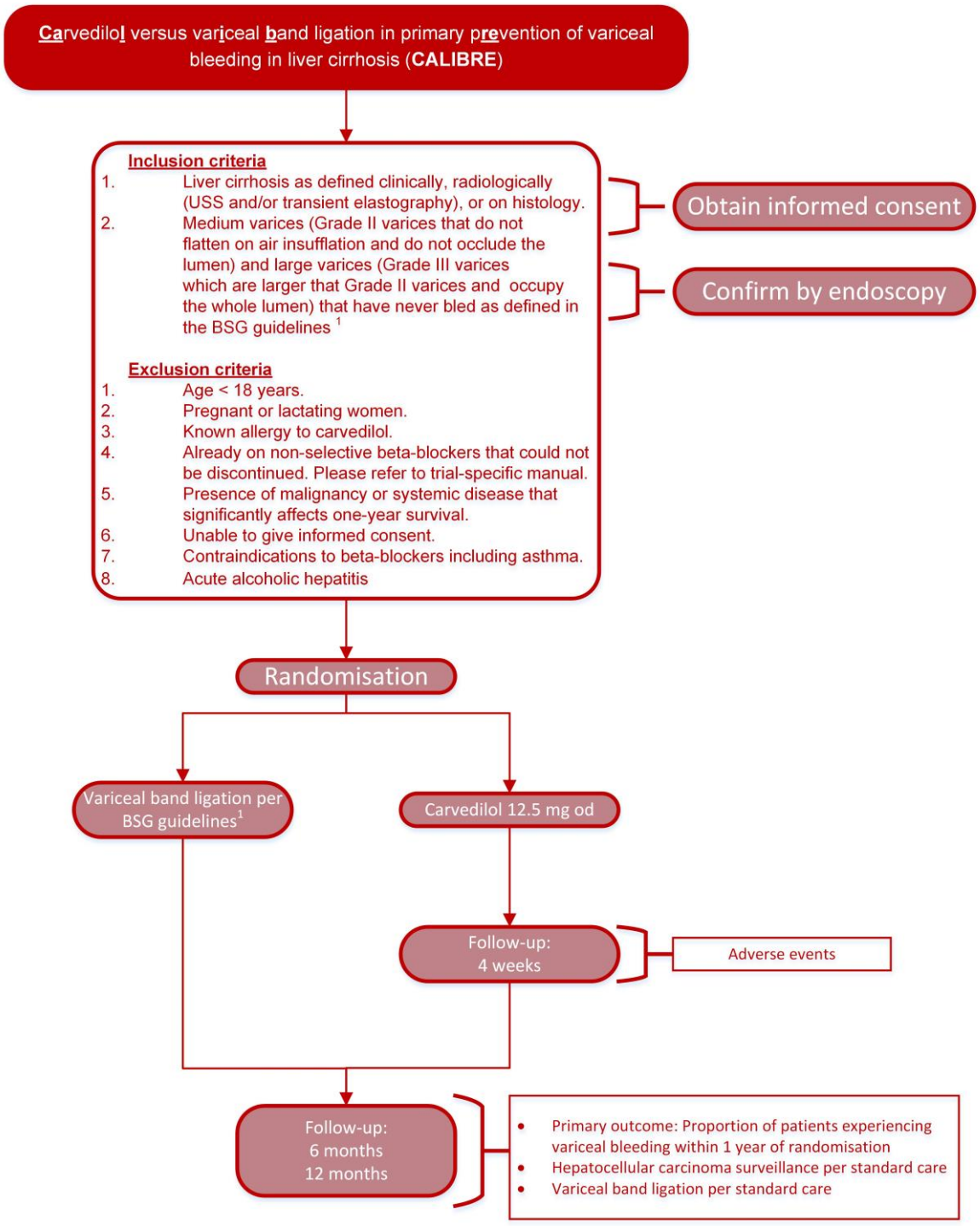
TRIAL SUMMARY

Title	**Carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis**
Acronym	**CALIBRE**
Trial Design	A multicentre, pragmatic, randomised controlled, open-label, two-arm parallel group trial with internal pilot.
Aim	To investigate the clinical and cost-effectiveness of carvedilol versus variceal band ligation in patients with cirrhosis and medium to large oesophageal varices that have never bled
Interventions	Carvedilol 12.5 mg od Variceal band ligation
Total number participants	2630 patients (1:1 randomisation) based on detecting a 33% proportional improvement from 12% to 8% in the 1-year variceal bleeding rate – a superiority hypothesis with power 90%, two-sided alpha 0.05 and allowing for 10% dropout.
Planned trial sites	Acute NHS Trusts and Health Boards in the UK
Main inclusion and exclusion criteria	**Inclusion criteria:** 1. Liver cirrhosis as defined clinically, radiologically (USS and transient elastography) or on histology. 2. Medium varices (Grade II varices that do not flatten on air insufflation and do not occlude the lumen) and large varices (Grade III varices which are larger that Grade II varices and occupy the whole lumen) that have never bled as defined in the BSG guidelines. [1] **Exclusion Criteria:** 1. Age < 18 years. 2. Pregnant or lactating women. 3. Known allergy to carvedilol. 4. Already on non-selective beta-blockers that could not be discontinued. 5. Presence of malignancy or systemic disease that significantly affects one-year survival. 6. Unable to give informed consent. 7. Contraindications to beta-blockers including asthma. 8. Acute alcoholic hepatitis.

Outcome measures	**Primary outcome:**
	
	Any variceal bleeding within one year of randomisation
	
	Secondary outcomes:
	
	1. Time to first variceal bleed in days from randomisation
	2. Mortality at one year (from randomisation):
	  a. All-cause mortality
	  b. Liver related mortality
	  c. Cardiovascular mortality
	3. Transplant free survival at one year (from randomisation)
	4. Adverse events related to treatment (up to 12 months after randomisation):
	  a. Dysphagia
	  b. Symptomatic hypotension
	  c. Dyspnoea
	  d. Gastrointestinal upset
	5. Other complications of cirrhosis:
	  a. New onset ascites
	  b. New onset encephalopathy
	  c. Spontaneous bacterial peritonitis
	  d. Hepatocellular carcinoma
	  e. Any renal dysfunction
	6. Health-related quality of life (EQ-5D-5L) from randomisation to six and 12 months.
	7. Use of healthcare resources, costs and cost-effectiveness based on the outcomes of cost per variceal bleeding avoided within one year of randomisation, cost per Quality-Adjusted Life-Year (QALY) estimated using the EQ-5D-5L, and cost per death avoided at one year.
	8. Patient preference. We will conduct qualitative interviews with patients in the pilot study. These interviews will explore patients' experience of and preferences related to treatment (Carvedilol or VBL). This will provide the basis to describe qualitatively patients' experience of trial interventions. This qualitative data will complement quantitative outcome assessment.
	9. Use of alternative therapies.
	10. Crossover therapies.

Trial duration per participant	Total follow up of 12 months per participant.

TRIAL SCHEMA



[1]Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, Austin A, Ferguson JW, Olliff SP, Hudson M, Christie JM; Clinical Services and Standards Committee of the British Society of Gastroenterology. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut. 2015 Nov;64(11):1680-704.

1 Background and Rationale

1.1 Existing Research and Current Practice

Liver disease is the 5th largest cause of death in the UK, with mortality predicted to double in 20 years. Patients with liver disease die younger with the average age of death of 59 years, compared with 82-84 years for heart and lung disease and stroke. In England, in total 30,000–60,000 patients are at risk or affected by liver cirrhosis. One of the major complications of cirrhosis is portal hypertension and variceal bleeding. In patients with cirrhosis, varices develop at a rate of 5% per year with 10 year cumulative incidence of 44%.[1] At least 3,000 patients are admitted to hospital in England per year with variceal bleeding, with inpatient mortality of 15% and one year mortality of up to 40%. Increased hospitalisation results in increased use of secondary care and substantial health care costs. Since many patients are of working age there are also significant workforce implications. Therefore, reducing the risk of the first variceal bleed (primary prevention), is an important clinical, and economic goal.

At present there are two options for primary prevention of variceal bleeding, namely non-selective beta-blockers and variceal band ligation. Beta-blockers used for portal hypertension in the UK are propranolol and carvedilol. A Cochrane meta-analysis of 19 trials (1504 patients) comparing variceal band ligation versus beta-blockers showed reduced variceal bleeding with variceal band ligation (risk ratio [RR], 0.67; 95% confidence interval [CI], 0.46–0.98) with no effect on survival.[2] However, the quality of evidence was low to moderate. Furthermore, when only high quality trials (7 trials, 713 patients) with minimum bias and good follow up were studied the difference in bleeding rates disappeared. In another meta-analysis, although adverse events were more frequent with beta-blockers (OR 2.61, 95% CI 1.60-4.40, $P < 0.0001$), fatal adverse effects were significantly lower with non-selective beta-blockers (NSBB; OR 0.14, 95% CI 0.02–0.99 $p < 0.05$).[3] The fatalities relate to banding induced bleeding from ulcers. No adverse events from beta-blockers such as symptomatic hypotension, dyspnoea, and gastrointestinal upset directly resulted in death.

1.2 Trial Rationale

The main focus of the research is the comparison of beta-blockers and variceal band ligation in the prevention of the first variceal bleed. A large randomised controlled trial at this time would help clinicians decide on the best treatment as the current evidence is based on underpowered and low quality trials as detailed above.

Carvedilol has been selected as the beta-blocker for this trial. Propranolol is not always well tolerated, and a third of patients fail to achieve a satisfactory reduction in portal pressure. Therefore, there is considerable interest in alternatives to propranolol, such as carvedilol. Carvedilol is well tolerated and in addition has vasodilating actions due to alpha-1 receptor blockade. The latter

reduces portocollateral resistance, and by actions on hepatic stellate cells leads to reduced intrahepatic resistance. Haemodynamic studies demonstrate a greater reduction in portal pressure than propranolol, and carvedilol can be effective even in patients not responding to propranolol.[4] Carvedilol also has anti-inflammatory, anti-oxidant, and antifibrotic properties along with other roles in enhancing insulin sensitivity and improving mitochondrial function.[5] A recent randomised placebo controlled trial of 140 patients showed that carvedilol reduced progression of varices over a minimum of 24 months follow up in patients with small varices, with no difference in bleeding or survival.[6] There are only two randomised controlled trials of carvedilol versus variceal band ligation in primary prevention.[7,8] The first trial from the UK of 152 patients showed significantly reduced bleeding in the carvedilol arm (10% versus 23%, relative hazard 0.41; 95% CI 0.19-0.96), with no apparent effect on survival (35% versus 37%, relative hazard 0.91; 95% CI 0.53-1.55).[8] The second trial from Pakistan of 168 patients did not show any differences in bleeding (8.5% versus 6.9%, relative hazard 1.61; 95% CI 0.27-9.69) or mortality (12.8% versus 19.5%, relative hazard 1.53; 95% CI 0.71-3.30).[7] Compliance with variceal band ligation was better in the second trial, and unlike the first trial, there were significantly more patients with viral hepatitis than alcoholic cirrhosis which does not reflect the demographics of the UK. At present there are no studies comparing carvedilol with propranolol in primary prevention. A recent meta-analysis highlighted the lack of evidence for carvedilol in primary prevention.[9]

Many specialists have significant concerns about the adverse effects of variceal band ligation in primary prevention of variceal bleeding in particular the risk of banding induced bleeding.[2,3] Likewise there are also concerns about the use of beta-blockers in patients with advanced cirrhosis with some studies showing higher mortality[10,11] while others report improved survival.[12] In particular with carvedilol, improved survival has been suggested.[13] None of these studies are randomised controlled trials (RCTs) and are limited by their retrospective nature and potential for selection and confounding bias.

Data on cost effectiveness in the context of primary prevention is available from just one publication.[14] This suggested beta-blockers have reduced overall costs compared with variceal band ligation. However, in the 2016 the National Institute for Health and Care Excellence (NICE) cirrhosis guidelines after extrapolation of the meta-analysis showing less bleeding with variceal band ligation, variceal band ligation was found to be more cost effective.[15] There are no cost effectiveness studies alongside a RCT comparing carvedilol with variceal band ligation.

There have been two important guidelines published in the UK in 2015-2016 from NICE and the British Society of Gastroenterology (BSG).[1,15] NICE favours banding for primary prevention, whereas the British Society of Gastroenterology (BSG) suggests banding if intolerant of beta-blockers. Therefore, there is at present disparity in the current UK guidelines with regards to first line therapy for primary prevention.

The results of this trial will provide high quality data with adequate power and follow up. If carvedilol is found to be superior to variceal band ligation then it will become first line therapy in primary prevention. The trial will also provide a unique cohort to follow-up using routine data to help us understand the long-term impact of beta-blockers. It is plausible that survival may also be better with carvedilol than for variceal band ligation as has been suggested in a study of beta-blockers in secondary prevention.[16] If this is true, it will lead to a paradigm shift in primary prevention of variceal bleeding. Such a finding will also encourage further research into the underlying mechanisms.

Beta-blockers as first line therapy in primary prevention will lead to a large change in practice since NICE guidance presently recommends variceal band ligation. This can have positive effects for the NHS and patients since beta-blockers require much less NHS resources. As a result of reduced need for variceal band ligation for primary prevention, which usually requires at least 2 treatments and indefinite endoscopic surveillance, the resource saved could be used for other procedures within the NHS. There is no requirement for patients on carvedilol for primary prevention to undergo endoscopic surveillance.[1] Bed pressures for other elective procedures could be eased and waiting times improved.

1.3 Justification for Participant Population

The present UK guidelines recommend primary prevention against variceal bleeding only in adult patients with Grade II or larger varices based on the current evidence. There is insufficient evidence to support treating patients with no or small (Grade I) varices.[1,15] Patients with acute alcoholic hepatitis will be excluded because not all of them will have cirrhosis and the condition itself has a significant effect on portal pressure which would be a confounding factor. The British National Formulary advises caution on prescribing carvedilol during pregnancy and lactation due to lack of safety information, hence pregnant and lactating patients are excluded from CALIBRE.

1.4 Justification for Design

The trial is a pragmatic RCT which mirrors standard care in the UK.[1,15] Due to the two interventions under study being so different (drug versus endoscopic variceal band ligation) it is not feasible to have a blinded design. Additionally, given that patients with Grade II or larger varices must be treated, sham therapy and placebo were considered infeasible.

1.5 Internal Pilot Trial

The first 12 months of the recruitment period of the **CALIBRE** trial will constitute an internal pilot to assess and confirm logistics and to determine if it is both feasible and practical for the trial to

continue. The results of the internal pilot will be assessed by the Trial Steering Committee and the funder.

1.6 Choice of Interventions

Since carvedilol appears a more potent beta-blocker than propranolol with potential for better clinical efficacy, is well tolerated, administered once daily and of lower cost (at the time of writing, £0.95 versus £1.70 (propranolol) per month; BNF costs in 2018), it seems the more appropriate drug to study in the setting of primary prevention.

Variceal band ligation is the only current treatment alternative to non-selective beta blockers for primary prevention of variceal bleeding in patients with Grade II or larger oesophageal varices.

2. Aims and Objectives

2.1 Primary Objective

To compare carvedilol versus variceal band ligation in preventing any variceal bleeding within 1 year of randomisation in patients with cirrhosis and medium to large oesophageal varices that have never bled.

2.2 Secondary Objectives

To investigate the effect of carvedilol and variceal band ligation on survival, development of other complications of cirrhosis and adverse events.

To assess cost-effectiveness, patient preference and use of alternative or cross over therapies.

2.3 Progression Criteria

- At the end of the 12-month pilot phase, the following targets should be met to justify progression to the main trial:
- Minimum of 250 participants recruited across the 20 sites with 2 sites opening per month and an average of 1.6 patients per month per open site.
- 90% of patients complete data collection at their six months follow-up visit.
- Trial Steering Committee and Data Monitoring Committee report no safety concerns which would prohibit continuation to main trial.

3. Trial Design & Setting

3.1 Trial Design

A multicentre, pragmatic, randomised controlled, open-label, two-arm parallel group trial with internal pilot.

3.2 Trial Setting

Approximately 66 Acute NHS Trusts/ Health Boards in the UK.

3.3 Identification of participants

Participants may be identified and recruited in one of the following ways (please also refer to Section 6.1):

- By their Specialist Liver Consultant or Research Nurse in advance of standard of care variceal surveillance endoscopy.
- Referral from an outpatient clinic following a diagnostic endoscopy.
- Identification from inpatient referrals.

3.4 Qualitative Research

We will conduct qualitative research within the pilot phase, with patients and staff to assess the feasibility and acceptability of the trial and the intervention(s) and to inform the main trial. With the participant's consent, we will interview (semi-structured interview) a sample of patients participating in each arm of the trial, patients who declined to take part in the trial, and staff who are involved in the trial. Participants will be provided with an ethically-approved patient information sheet (PIS) outlining the purpose of the interviews and what it will involve for them. If participants are willing to be interviewed, verbal consent will be obtained prior to commencement of the interview. The researcher will read each of the statements detailed on the ethically-approved informed consent form (ICF) asking participants to confirm that they understand and provide consent. This consent process will be audio-recorded and the researcher will also keep a written record of this on a printed ICF. Participants in each arm of the trial will be interviewed soon after randomisation and once again between six and 12 months following randomisation. One-to-one interviews with participants will be conducted in their home, either in person, over the telephone, or by Skype, as preferred by participants, although logistical constraints (e.g. travelling, geography) may preclude some face-to-face interviews. Patients declining entry to the trial but agreeing to participate in an interview regarding this will take part in a one-off interview.

The main aim of the interviews (participants and staff) is to ensure the feasibility of recruitment. For this, we will focus on the recruitment process, the patients' motivations for taking part or not in the trial, and the barriers and facilitators to patients' participation in the trial. Follow up interviews with patients will focus on their experience of treatment (carvedilol or variceal band ligation) and of trial processes. Data collection and analysis will proceed iteratively until the research team judge that the data and sample have sufficient depth and breath.[17] Experience from previous studies indicates that a sample of approximately 30-35 patients is sufficient to achieve this. Data from this qualitative research will provide in-depth understanding of patients' and staff members' preferences related to the recruitment processes, helping us identify potential difficulties quickly before the main trial.

Analysis of qualitative data: Interviews will be recorded with the consent of participants and transcribed clean verbatim for analysis. Analysis will be conducted with reference to recordings, transcripts and field notes taken at the time of data collection. A thematic analysis of content will be informed by the Framework analytical approach.[18] Following initial familiarisation with the interview data, development of thematic frameworks and data coding will proceed in an iterative manner. Data collection and analysis will run concurrently so that emergent analytical themes can inform further data collection, and particularly comparative analytical questioning between patients allocated to carvedilol and variceal band ligation.

3.5 Health Economics

The economic evaluation will determine the relative cost-effectiveness of carvedilol compared with variceal band ligation in patients with liver cirrhosis. A within-trial analysis will be conducted from a National Health Service and Personal Social Services (NHS/PSS) perspective, as per recommended guidelines,[19] based on the outcomes of cost per variceal bleeding avoided within one year of randomisation, cost per Quality-adjusted Life-year (QALY) estimated using the EQ-5D-5L, and cost per death avoided. These three outcomes were considered important from a clinical and policy point of view and were selected to allow a comprehensive assessment of cost-effectiveness and to avoid any potential loss of opportunity. Prevention of variceal bleeding is the primary outcome of the clinical trial, and therefore it was important to evaluate the cost-effectiveness of carvedilol based on this outcome. The use of quality-adjusted life-years in economic evaluations is recommended by the National Institute for Health and Care Excellence (NICE) in order to allow comparisons of cost-effectiveness across different diseases and interventions. If carvedilol is shown to prevent deaths from variceal bleeding, this will also be a very important outcome to include in our economic analysis.

Information on health care resource use required to deliver the interventions (carvedilol, variceal band ligation) will be collected within the trial. Resource use information associated with the treatment of variceal bleeding and follow-up care whilst an inpatient, admission to an intensive care unit, treatment of adverse events and other complications, readmissions, and primary care contacts

will be prospectively collected at regular follow-up hospital appointments. Unit cost data will be obtained from national sources,[20] and other secondary sources where appropriate. To account for the skewed distribution commonly seen in economic data and the uncertainty around cost-effectiveness point-estimates, bootstrap methods will be used in the analysis.[21] 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.[22]

If there is evidence, from the trial or the literature that differences between carvedilol and variceal band ligation exist, in terms of re-bleeding or mortality rates as well as other outcomes that may have significant cost or outcome implications beyond the trial period, a model-based economic evaluation will additionally be conducted. This will ensure that all important costs and benefits are taken into account in economic analysis. Depending on data availability, the analysis will be conducted from the NHS/PSS perspective, using a lifetime horizon and recommended discounting adjustments. 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.

3.6 Assessment of Risk

The assessment and management of risk is detailed in the separate **CALIBRE** Risk Assessment document.

Both beta-blockers and variceal band ligation are presently used as standard of care. The risk profile of both is well established.

This trial is categorised as:

Type A = No higher than the risk of standard medical care

An on-going evaluation of risk will continue throughout the trial.

4. Eligibility

4.1 Inclusion Criteria

To be eligible to participate in the **CALIBRE** Trial, patients must have both:

- Liver cirrhosis as defined clinically, radiologically (USS and transient elastography), or on histology

  and
- Medium varices (Grade II varices that do not flatten on air insufflation and do not occlude the lumen) and large varices (Grade III varices which are larger than Grade II varices and occupy the whole lumen) that have never bled as defined in the BSG guidelines [1]

***Note**:*

Patients with portal vein thrombosis of any grade can be included in **CALIBRE**

4.2 Exclusion Criteria

If any of the following applies, the patient is not eligible to be randomised into the CALIBRE Trial:

- Age < 18 years
- Pregnant or lactating women
- Known allergy to carvedilol
- Already on non-selective beta-blockers that could not be discontinued.
- Presence of malignancy or systemic disease that significantly affects 1 year survival
- Unable to give informed consent
- Contraindications to beta-blockers including asthma
- Acute alcoholic hepatitis

4.3 Co-Enrolment

The Trial Management Group (TMG) will consider requests for co-enrolment into other trials in accordance with best practice recommendations. This will ensure careful consideration of patient burden, compatibility of interventions, organisational issues and follow-up. A log of co-enrolled patients will be maintained by BCTU.

5. Informed Consent Procedure

It will be the responsibility of the Investigator to obtain written informed consent for each participant prior to performing any trial related procedure. Consent may also be taken by other members of the site research team (e.g. Research Nurse) if local practice allows and this responsibility has been delegated by the Principal Investigator (PI) as captured on the Site Signature and Delegation Log.

A Participant Information Sheet (PIS) will be provided to facilitate this process. Investigators or their delegate(s) will ensure that they adequately explain the aim, trial treatments, anticipated benefits and potential hazards of taking part in the trial to the participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time. The participant will be given adequate time to read the PIS and to discuss their participation with others outside of the site research team. The participant will also be given the opportunity to ask questions. If the participant 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 participant must give explicit consent for the regulatory authorities, members of the research team and or representatives of the sponsor to be given direct access to the participant's medical records.

The Investigator or delegate(s) will then sign and date the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the Investigator Site File (ISF), a copy will be sent to BCTU and the original placed in the participant's medical notes. Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant and version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant 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 participants' decision to continue, participants will be given time to consider and if happy to continue may be re-consented depending on the nature of the new information. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

This trial will include optional consent to allow linkage to patient data available in NHS routine clinical datasets, including primary care data (e.g. Clinical Practice Research Datalink; CPRD, The Health Improvement Network; THIN, QResearch), secondary care data (Hospital Episode Statistics; HES) and mortality data from the Office of National Statistics (ONS) through NHS Digital and other central UK NHS bodies. The consent will also allow access to other new central UK NHS databases that may appear in the future. This will allow us to double check the main outcomes against routine data sources, and extend the follow-up of patients in the trial and collect long-term outcome and health resource usage data without needing further contact with the trial participants. This is important, as it will link a trial of treatments that may become a clinical standard of care to long-term outcomes that are routinely collected in clinical data, but which may not be collected during the period of the trial.

Electronic copies of the PIS and ICF will be available from the **CALIBRE** Trial Office. Details of all patients approached about the trial will be recorded on the Participant Screening/Enrolment Log.

6. Recruitment and Randomisation

6.1 Recruitment

In the **CALIBRE** trial, a medically qualified doctor who is delegated the task on the **CALIBRE** trial delegation log will confirm eligibility prior to randomisation.

Participants may be identified and recruited in one of the following ways:

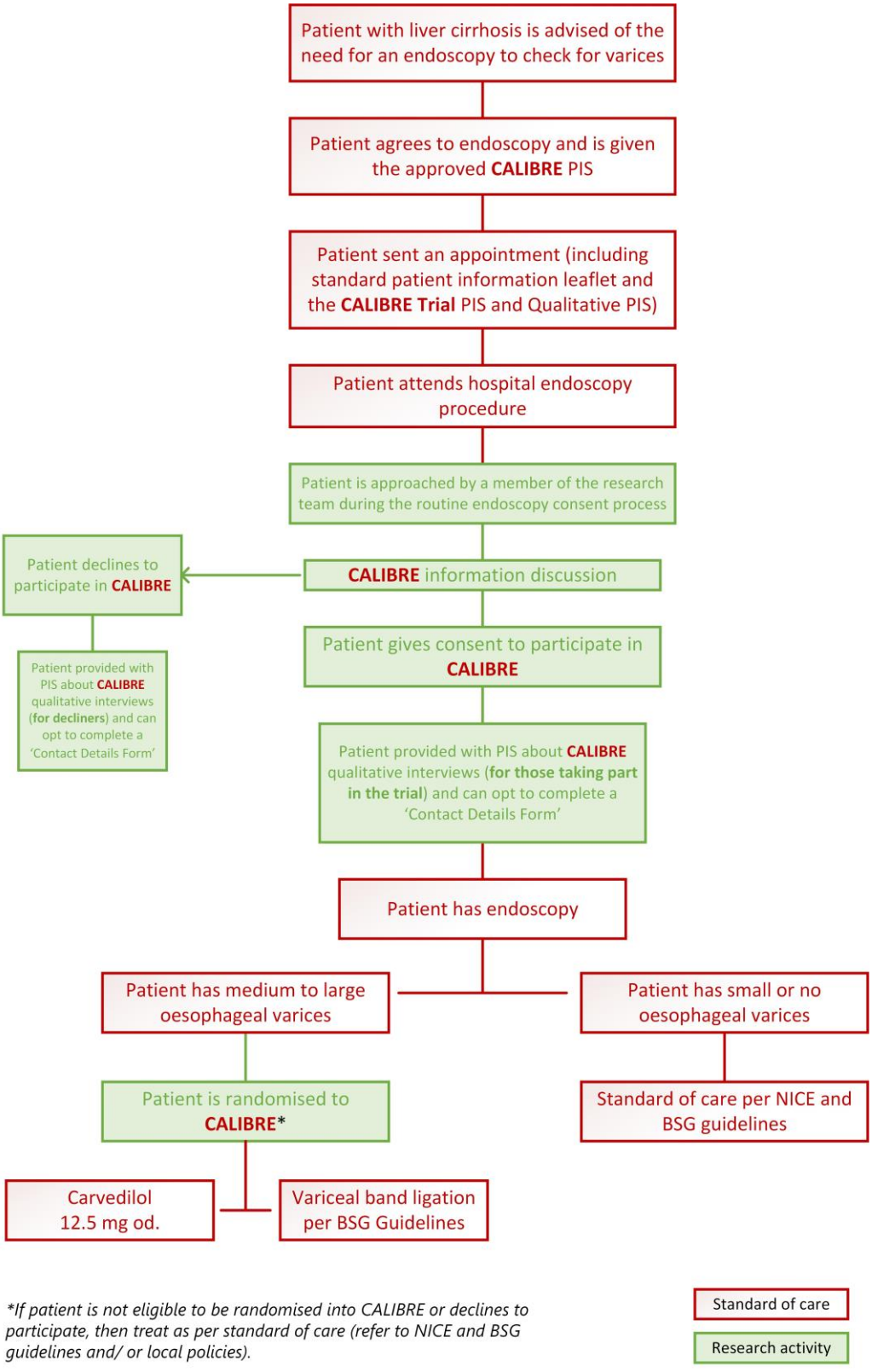
6.1.1 Planned Endoscopy Where No Diagnosis of Varices Has Yet Been Made

By their Specialist Hepatology/Gastroenterology Consultant or Nurse. Potential participants will be provided with an ethically approved patient information sheet (PIS) along with other information relating to planned surveillance endoscopy. The PIS will be provided in clinic or posted to the patient in advance of planned endoscopy by their Specialist Hepatology/ Gastroenterology Consultant or Research Nurse. On the day of their planned, standard-care endoscopy, they will then be asked if they are willing to provide informed consent to participate in **CALIBRE**. If they are then found to have grade II or larger varices on endoscopy they will be eligible for randomisation during the same endoscopy session. Participants who have provided consent and are found to be eligible (**Figure 1**) will have baseline assessments (which will be supplemented by results of blood tests and observations from clinical records), recorded on the Baseline CRF.

If the potential participant is found to be not eligible (i.e. they do not have grade II or larger varices on endoscopy), the site should keep a copy of the potential participants signed ICF (this should **not** be sent to the **CALIBRE** Trial Office) and document in the potential participant's medical records

that they were not eligible to be randomised into **CALIBRE**. This should also be documented on the **CALIBRE** Screening Log.

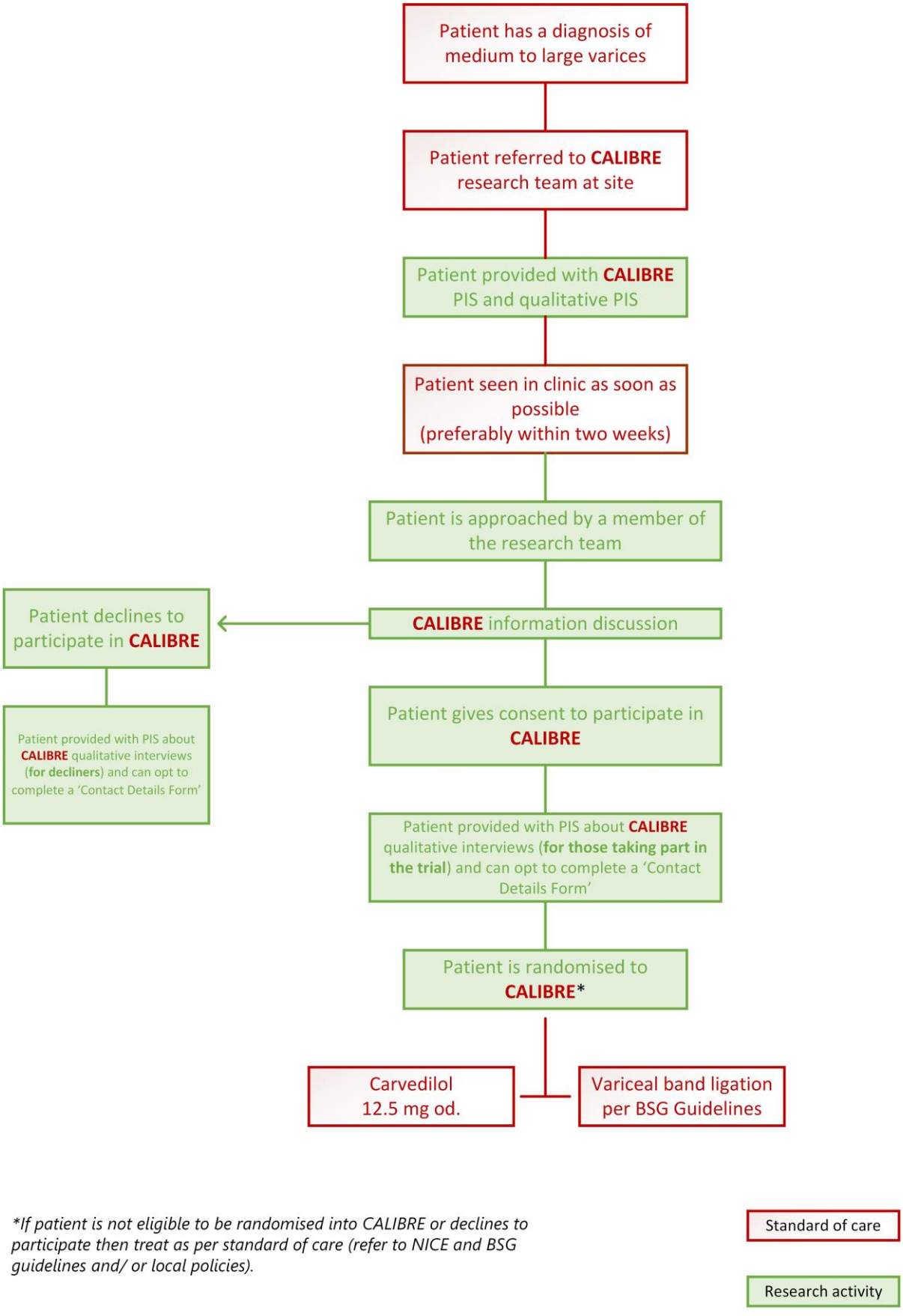
Figure 1: Consent process (planned endoscopy where no diagnosis of varices has yet been made



6.1.2 Referral from an Outpatient Clinic Following Diagnostic Endoscopy

Where medium or large varices have already been diagnosed but no treatment has yet been given, the PIS will be provided to potential participants during their usual care outpatient visit, or sent to them in advance of their planned usual care outpatient visit. If they meet eligibility criteria and are willing to participate, they will be consented (**Figure 2**) and randomised. The baseline assessments will also be completed at this visit. If the participant is randomised to the VBL arm, then per standard care, an endoscopy will be arranged as soon as possible, preferably within two weeks of this visit.

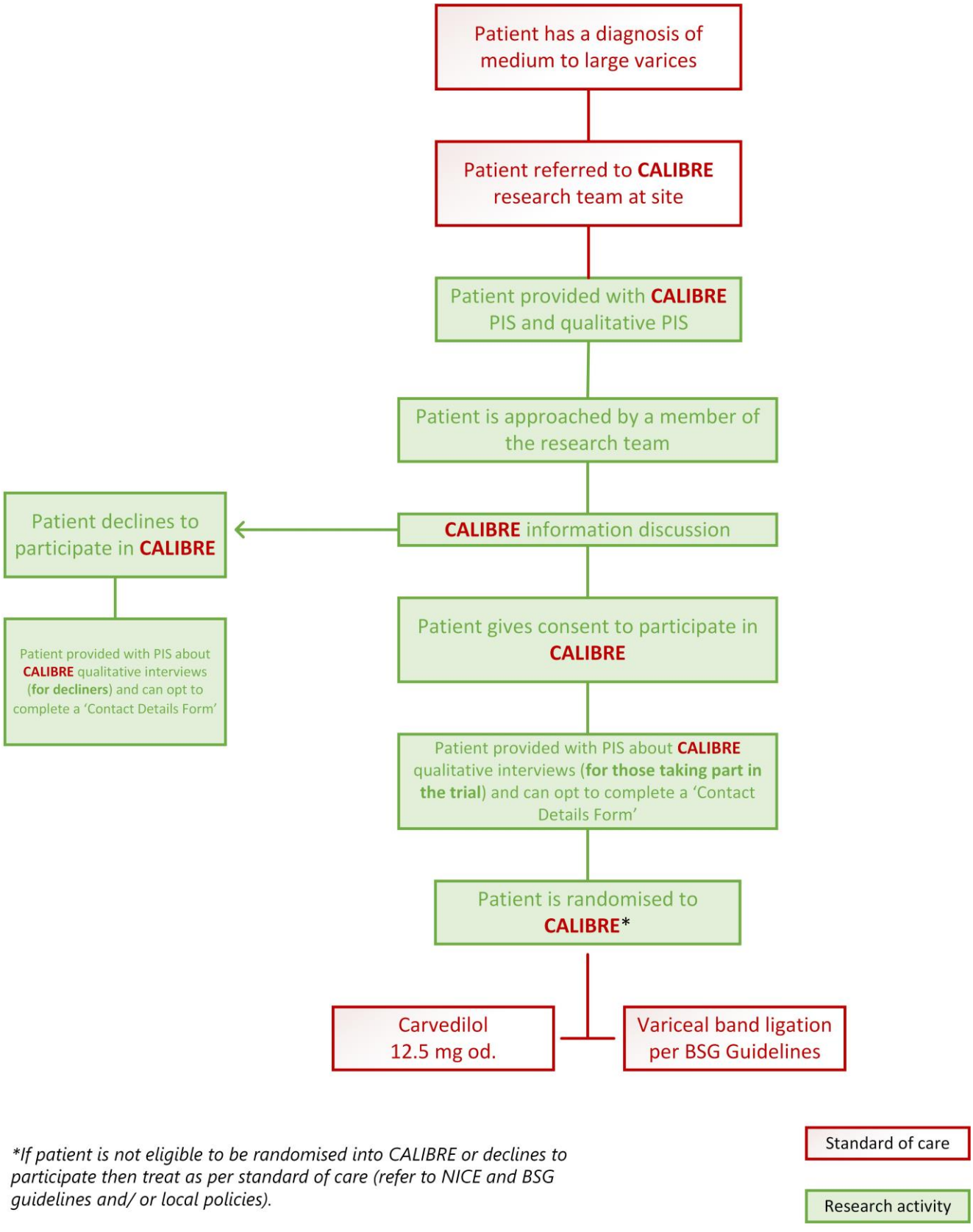
Figure 2: Consent process following referral from an outpatient clinic following diagnostic endoscopy



6.1.3 Identification from Inpatient Referrals

Where medium or large varices have been diagnosed at endoscopy but no treatment has been started, potential participants will be provided with an approved PIS during their inpatient stay. If they meet eligibility criteria and are willing to participate, they will be consented (**Figure 3**) and randomised. Baseline assessments will take place on the day of randomisation by extracting relevant data from routine medical notes and electronic patient data where applicable. If the participant is randomised to the VBL arm, then an endoscopy will be arranged as soon as possible, preferably within two weeks of randomisation.

Figure 3: Consent process following an inpatient referral



**If patient is not eligible to be randomised into CALIBRE or declines to participate then treat as per standard of care (refer to NICE and BSG guidelines and/ or local policies).*

6.2 Randomisation

Randomisation will be provided by a secure online randomisation system at BCTU. Unique login usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the study as detailed on the **CALIBRE** Trial Signature and Delegation Log. The online randomisation system will be available 24 hours a day, seven days a week, apart from short periods of scheduled maintenance. A telephone toll-free randomisation service (0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days.

After participant eligibility has been confirmed and informed consent has been received, the participant can be randomised into the trial. A Randomisation Form will be provided to investigators and will be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Form must be answered before a Trial Number can be given. If data items are missing, randomisation will be stopped, but can be restarted once the information is available. Only when all eligibility criteria and baseline data items have been provided will a Trial Number be allocated.

Participants will be randomised at the level of the individual in a 1:1 ratio to either treatment with 12.5 mg carvedilol od or variceal band ligation. Both of these treatments will start on the same day as randomisation, or as soon as possible after. Patients randomised in clinic after the diagnostic endoscopy will be started on carvedilol 12.5mg od or variceal band ligation within two weeks of randomisation. A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the following variables: presence or absence of hepatic decompensation (ascites or encephalopathy), size of the largest varix (Grade II, or Grade III), age of patient at randomisation (18-50, 51-70, >70), and presence or absence of alcohol related liver disease.

A ‘random element’ will be included in the minimisation algorithm, so that each patient has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received. Full details of the randomisation specification will be stored in a confidential document at BCTU.

Following randomisation, a confirmatory e-mail will be sent to the randomising clinician and BCTU **CALIBRE** trial inbox.

The Investigator will keep and maintain the **CALIBRE** Screening Log which will be kept in the ISF, and an anonymised version should be available be sent to Trial Office upon request.

6.3 Informing Other Parties

With the participant's prior consent, their General Practitioner (GP) will also be informed that they are taking part in the trial.

6.4 Blinding

Due to the two interventions under study being so different (drug versus endoscopic variceal band ligation), it is not feasible to have a blinded design. 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 clearly defined according to the BSG guidelines[1] which involves an objective assessment of the presence or absence of upper gastrointestinal bleeding, supplemented by laboratory results.

7. Trial Treatment/Intervention

7.1 Trial Treatments

7.1.1 Carvedilol

Participants will be prescribed 12.5mg od for up to 12 months. They will be seen in a follow up clinic at four weeks to assess for any short term adverse events such as symptomatic hypotension, gastrointestinal side effects like nausea, and shortness of breath.[1] These patients will not be offered routine endoscopic surveillance, as per standard of care. [1]

7.1.2 Variceal Band Ligation

The procedure will be performed as per the British Society of Gastroenterology guidelines.[1] Varices are banded at regular intervals (usually two to four weekly) until they are eradicated when they are normally replaced by scar tissue or by varices of much smaller size. Patients usually require on average 2-3 banding procedures to achieve eradication. After successful eradication of the varices, patients have a repeat endoscopy at approximately three months, then at approximately six monthly thereafter. Any recurrent varices (i.e. medium to large varices) are treated with further variceal band ligation until eradication and then offered repeat endoscopy at approximately six monthly intervals.

7.2 Drug interaction or Contraindications

Contraindications to carvedilol are as listed in the British National Formulary: asthma; cardiogenic shock; hypotension; marked bradycardia; metabolic acidosis; phaeochromocytoma (apart from specific use with alpha-blockers); Prinzmetal's angina; second-degree AV block; severe peripheral

arterial disease; sick sinus syndrome; third-degree AV block; uncontrolled heart failure. A full list on interactions with carvedilol is listed in the British National Formulary.

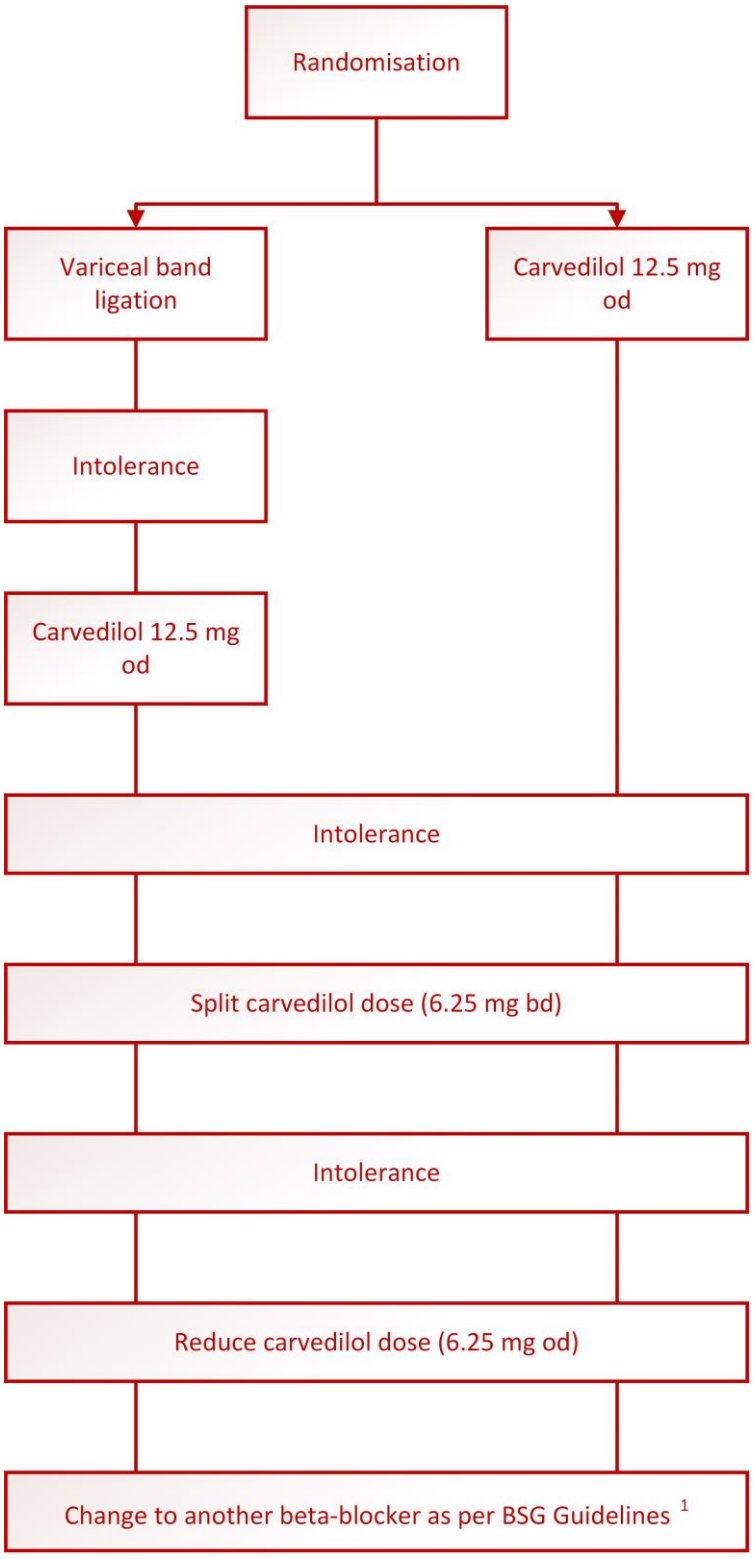
7.3 IMP Accountability Procedures and Labelling

Through the risk-adapted approach, a full risk assessment of the **CALIBRE** trial has been conducted including the drug accountability requirements. Carvedilol will be used within its authorisation, prescribed on an NHS prescription and dispensed by a pharmacy from standard stock. The risk assessment has determined that a normal dispensing label is appropriate and an additional clinical trial label is not necessary (as covered by Regulation 46 (2) of SI 2004/1031). Drug accountability will be according to standard practice for NHS prescriptions. Details of how adherence will be assessed for those participants randomised to the carvedilol arm can be found in **Section 7.7**.

7.4 Treatment Modification

Figure 4 outlines the process for treatment modifications in the event of intolerance. At clinician's discretion participants that are intolerant of carvedilol or variceal band ligation can be crossed over to the other arm at any point.

Figure 4: Schemata of therapies



7.5 Discontinuation of Trial Treatment

Participants may discontinue trial treatment at any point if they choose to or if their clinical team feel that continued treatment within the trial is inappropriate.

Participants who do discontinue trial treatment will be asked if they are still willing to be followed-up as part of the trial.

Discontinuation of trial treatment will be documented on the Follow-Up CRFs.

7.6 Treatment Storage

Carvedilol may be dispensed from standard stock by both the pharmacy at the research site and community pharmacies local to the participant. Carvedilol will be used as per standard clinical practice and so there is no additional requirement, above that of local policy, to monitor temperature during storage. Drugs that have expired or are returned as excess drug should be destroyed in accordance with local practice.

7.7 Assessment of Adherence

7.7.1 Carvedilol Arm

Participants will be asked about adherence with their trial medication at each follow-up visit and their response documented in the medical notes and subsequently transcribed onto the Follow-Up CRFs.

7.7.2 Variceal Band Ligation

Adherence to variceal band ligation will be documented on the Follow-Up CRFs using information available in the participant's medical notes.

8. Outcome Measures and Study Procedures

8.1 Primary Outcome

Any variceal bleeding within 1 year of randomisation*.

8.2 Secondary Outcomes

1. Time to first variceal bleed in days (from randomisation).
2. Mortality at one year (from randomisation):
   a. All-cause mortality.
   b. Liver related mortality.

c. Cardiovascular mortality.

3. Transplant free survival at one year (from randomisation).
4. Adverse events related to treatment (up to 12 months after randomisation):
    a. Dysphagia requiring discontinuation of treatment.
    b. Symptomatic hypotension requiring change in treatment.
    c. Dyspnoea.
    d. Gastrointestinal upset.
5. Other complications of cirrhosis:
    a. New onset ascites confirmed clinically or on imaging and graded as per ICA recommendations.[24] Please refer to Appendix.
    b. New onset encephalopathy defined using West Haven Criteria.[25] Please refer to Appendix.
    c. Spontaneous bacterial peritonitis
    d. Hepatocellular carcinoma.
    e. Any renal dysfunction as per International Club of Ascites – Acute Kidney Injury (ICA-AKI) definitions.[23] Please refer to Appendix. Health-related quality of life (EQ-5D-5L) at trial entry, six and 12 months.
6. Health-related quality of life (EQ-5D-5L) from randomisation to six and 12 months.
7. Use of healthcare resources, costs and cost-effectiveness based on the outcomes of cost per variceal bleeding avoided within one year of randomisation, cost per Quality-adjusted Life-year (QALY) estimated using the EQ-5D-5L, and cost per death avoided at 1 year.
8. Patient preference. We will conduct qualitative interviews with patients in the pilot study. These interviews will explore patients' experience of and preferences related to treatment (Carvedilol or VBL). This will provide the basis to describe qualitatively patients' experience of trial interventions. This qualitative data will complement quantitative outcome assessment.
9. Use of alternative therapies. Please refer to **Figure 4**.
10. Crossover therapies. Please refer to **Figure 4**.

**** Note:***
The first variceal bleed 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.[1]

8.3 Schedule of Assessments

Refer to Table 1 below:

Table 1: Table of Assessments

	Randomisation and Baseline	4 weeks* ± 1 week FU visit	6 months ± 2 months FU visit	12 months ± 2 months FU visit
Confirm eligibility	✓			
Seek informed consent	✓			
Randomisation	✓			
Medical history[#]	✓			
Medication review	✓	✓	✓	✓
Physical examination	✓*		✓*	✓*
Office blood pressure	✓	✓	✓	✓
Pulse	✓	✓	✓	✓
Standard care blood tests	✓*		✓*	✓*
Height	✓*			
Weight	✓*	✓*	✓*	✓*
Administer EQ 5D-5L	✓		✓	✓
Resource use (Follow-Up CRFs)			✓	✓
Dispense trial medication[¥ ∞]	✓			
Adverse event review and evaluation		✓	✓	✓
Adherence			✓	✓
Qualitative interviews[§]		✓		✓

#Including aetiology of liver disease and past medical history (diabetes, ischaemic heart disease, pulmonary disease).

*Taken from clinical records.

¥Carvedilol arm only.

∞Medication may initially be dispensed by site but can subsequently be dispensed by the participant's community pharmacy.

§Pilot phase only

8.4 Withdrawal

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.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial (or part of it) at any time.

Types of withdrawal are defined below:

- The participant would like to withdraw from trial intervention, but is willing to be followed up in accordance with the schedule of assessments and, 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).

- The participant would like to withdraw from the qualitative interviews (pilot phase only), but is willing to continue with the trial intervention and be followed up in accordance with the schedule of assessments and, using any central UK NHS bodies for long-term outcomes.

- The participant would like to withdraw from trial intervention and 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 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).

- The participant would like to withdraw from trial intervention and is not willing to be followed up in any way for the purposes of the trial and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis).

or

- The participant wishes to withdraw completely (i.e. from trial treatment and all follow up) and is not willing to have any of their data, including that already collected, to be used in any future trial analysis.

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data and should also be recorded on the Change of Status Form.

8.5 Baseline Visit

Participant's details of clinical examination and blood results will be taken from their medical notes as defined in the CRF. Refer to **Section 8.3.**

8.6 Four Weeks Follow-Up Visit (Carvedilol Arm Only)

Participants will have observations noted in **Table 1** and assessed for any adverse events related to carvedilol in particular symptomatic hypotension, dyspnoea, and gastrointestinal upset. Mechanisms will be in place to manage intolerance as detailed in **Figure 4**.

8.7 Six and 12 Months Follow-Up Visit

These will take place during the patient's standard outpatient visits and routine data will be collected. Further details are noted in **Table 1**.

8.8 Trial Duration

All participants in the trial will be followed-up for 12 months if appropriate. Participants in the carvedilol arm will receive treatment for 12 months. If participants have a variceal bleed during the 12 months, they will be managed according to standard guidelines and the trial follow-up will continue until 12 months after randomisation.

At the end of the 12 months, the participants may, as determined by their clinician, continue with their allocated treatment but it will not be considered part of the trial intervention.

9. Adverse Event Reporting

9.1 Definitions

Standard definitions of different types of AEs are listed in **Table 2:**

Table 2: Definition of standard terms

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product which is related (or for which a causal relationship cannot be ruled out) to any dose administered to that subject
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: • In the case of a product with a marketing authorisation, in the summary of product characteristics for that product; • In the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
Serious adverse event (SAE), serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR)	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • Results in death; • Is life-threatening; • Requires hospitalisation or prolongation of existing hospitalisation; • Results in persistent or significant disability or incapacity; or consists of a congenital anomaly or birth defect
SUSAR	Suspected Unexpected Serious Adverse Reaction (as defined above)

9.2 Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. The Investigator will assess the seriousness and causality (relatedness) of all applicable AEs experienced by the participant with reference to the reference safety information. This should be documented in the source data with reference to the approved reference safety information (**Section 4.8**, Undesirable Effects) of the SmPC for carvedilol (date: 15th September 2017) and the protocol for variceal band ligation.

9.3 Adverse Event Reporting

In the **CALIBRE** trial, carvedilol is categorised as the IMP and the pharmacovigilance reporting requirements that will be followed are described in this section of the protocol. However we will collect adverse events in both arms of the trial.

The safety profile for the trial interventions are well established so although the severity and causality of all AEs should be recorded in the participants medical notes, a strategy of targeted reporting (to the Sponsor) of AEs will not compromise the safety of participants. Only data on the following adverse events will be collected by the **CALIBRE** Trial Office (**Table 3**):

Table 3: Adverse Events

The AEs summarised in Tables 3 and 4 will be reported on the **CALIBRE** Follow-Up CRF (six and 12 months).

Arm	Event(s)
Variceal band ligation	Abdominal pain
	Banding-related dysphagia
	Banding-related bleeding
Carvedilol	Blurred vision
	Bradycardia
	Dizziness
	Gastrointestinal upset
	Headache
	Lethargy
	Symptomatic hypotension
	Upper respiratory tract infection
	Sexual dysfunction

9.4 Serious Adverse Events

9.4.1 Events That Do Not Require Reporting to the Sponsor

At whatever time they occur during an individual's participation, from randomisation to end of participant follow-up. The following are "protocol exempt" SAEs.

- **Pre-planned hospitalisation**
- **Hospital admissions lasting less than 24 hours**

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, throughout the participant's time on trial, including follow-up.

9.4.2 Events That Do Not Require Expedited Reporting to the Sponsor on a SAE Form

CALIBRE trial participants are likely to have significant co-morbidities and therefore the frequency of SAEs may be high. Most of the SAEs occurring in **CALIBRE**, will be anticipated in the sense that they are recognised and accepted complications/consequences of liver cirrhosis and/ or oesophageal varices.

The events outlined in **Table 4** are regarded as expected SAEs (i.e. are recognised complications/consequences of liver cirrhosis and/ or oesophageal varices). These events should be reported in the participant's medical notes and on the **CALIBRE** Follow-Up CRFs (six and 12 months) instead and will not be subject to expedited reporting (i.e. within 24 hours of the event) because such events will, by protocol definition, be unrelated and therefore rapid assessment of causality is not required.

Table 4: Events That Do Not Require Expedited Reporting on a SAE Form

Event	CRF
Variceal bleeding	Follow-up CRF (six and 12 months)
Hepatic encephalopathy	
Ascites	
Hepatocellular carcinoma	
Spontaneous bacterial peritonitis	
Hepatorenal syndrome	

9.4.3 Events That Require Expedited Reporting to the Sponsor on a SAE Form

Investigators will report all SAEs (except those listed in **Sections 9.4.1** and **Sections 9.4.2**) on a SAE Form within 24 hours of being made aware of the event.

9.5 Monitoring Participants Pregnancies

In the event that a participant becomes pregnant during the follow-up, period a Pregnancy Notification Form will be completed (providing the participant's details) and returned to the **CALIBRE** Trial Office.

Details of the outcome of the pregnancy will be provided on a follow-up pregnancy notification form. A congenital anomaly or birth defect will be reported as an SAE and in compliance with Section 9.1.

There is no risk identified from male patients taking carvedilol whose partner subsequently becomes pregnant.

9.6 Reporting Period

Details of the targeted AEs will be documented and reported from the date of randomisation until administration of the last protocol-defined treatment.

9.7 Reporting Procedure for SAEs by Sites

Sites should report SAEs which are NOT listed as recognised complications of liver cirrhosis and/or oesophageal varices (as defined in **Section 9.4.2**), to the **CALIBRE** Trial Office on a SAE Form as soon as possible and no later than 24 hours after becoming aware of the event.

Completed SAE Forms can be faxed to the CALIBRE Trial Office on:
0121 415 8871 or 0121 415 9135

The research team at site will be required to respond to any related queries raised by the **CALIBRE** Trial Office as soon as possible.

Site Investigators should also notify their own Trust/ Health Board of any SAEs in accordance with their local policies.

For SAE Forms completed by someone other than the PI, the PI will be required to countersign the original SAE Form to confirm agreement with the categorisation of seriousness and causality assessments. The SAE Form should then be returned to the **CALIBRE** Trial Office and a copy retained at site.

9.8 Reporting Procedure – Trial Office

On receipt of the SAE form, the **CALIBRE** Trial Office will allocate each SAE a unique reference number which will be forwarded to the receiving hospital as proof of receipt. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE.

9.9 Assessment of Relatedness

On receipt of an SAE Form, seriousness and causality will be reviewed independently by the Chief Investigator (CI; or nominated delegate). In the carvedilol arm, a SAE judged to have a reasonable causal relationship with the trial intervention will be regarded as a Serious Adverse Reaction (SAR). In the band ligation arm a SAE judged to have a reasonable causal relationship with the trial intervention will be regarded as a related SAE. The causality assessment given by the PI will not be downgraded by the CI (or delegate(s)). If the CI (or delegate(s)) 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.

The CI (or nominated individual) will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the approved version of the Reference Safety Information) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

Table 5: Categorisation of causality

Category	Definition	Relatedness
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 (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events)	
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatments)	**Not related**
Not related	There is no evidence of any causal relationship	

9.10 Assessment of Expectedness

The CI or delegate(s) will also assess those SAEs that are not defined in this protocol as expected, with reference to the following criteria.

Table 4: Categorisation 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 this protocol.
Unexpected	An adverse event that is <u>not</u> consistent with known information about the trial related procedures.

9.11 Provision of Follow-up Information

Following reporting of an 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 **CALIBRE** Trial Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, the final version of the original SAE form completed at site must be returned to the **CALIBRE** Trial Office and a copy kept in the Site File.

9.12 Reporting to the Competent Authority and the Research Ethics Committee

9.12.1 Suspected Unexpected Serious Adverse Reactions

The **CALIBRE** Trial Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and REC within 7 days. Detailed follow-up information will be provided within an additional 8 days. All other events categorised as non-life threatening SUSARs will be reported within 15 days. A copy will be sent to the Trial Sponsor at the time of sending the SUSAR report.

9.12.2 Serious Adverse Reactions

The **CALIBRE** Trial Office will report details of all SAEs and SARs (including SUSARs) to the MHRA and REC annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR). A copy will also be sent to the Sponsor at the time of sending out the DSUR.

9.12.3 Adverse Events

Details of all AEs will be reported to the MHRA on request.

9.12.4 Other Safety Issues Identified During the Course of the Trial

The MHRA, REC and Sponsor will be notified immediately if a significant safety issue is identified during the course of the trial.

9.13 Investigators

Details of all SUSARs and any other safety issue(s) which arise during the course of the trial will be reported to Principal Investigators (PI). A copy of any such correspondence should be filed in the Investigator Site File (ISF).

9.14 Data Monitoring and Ethics Committee

The independent Data Monitoring and Ethics Committee (DMEC) will review all SAEs.

9.15 Developmental Safety Update Report

The **CALIBRE** Trial Office will provide the MHRA with DSURs. The reports will be submitted within 60 days of the Development International Birth Date (DIBD) of the trial each year until the trial is declared ended.

9.16 Annual Progress Reports

An Annual Progress Report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given and annually until the trial is declared ended. A copy will also be sent to the Sponsor at the time of sending out the DSUR.

9.17 Reporting Urgent Safety Measures

If any urgent safety measures are taken, the CI/BCTU shall immediately, and in any event no later than three days from the date the measures are taken, give written notice to the REC and MHRA of the measures taken and the circumstances giving rise to those measures.

10. Data Handling and Record Keeping

10.1 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 the subject, source data will be accessible and maintained.

Some data variables may be entered directly onto the CRF, these are clearly identified and detailed below.

Table 5: Source Data

Data	Source
Patient Reported Data (EQ-5D-5L)	The original participant-completed paper form is the source and will be forwarded directly to the **CALIBRE** Trial Office
Laboratory results	The original lab report, which may be electronic, is the source data and will be kept and maintained, in line with normal local practice.
Clinical event data	The original clinical annotation is the source data. 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 data.
Health economics (resource use) data	This will be completed on the Follow-Up CRFs via interview with the patient and/ or from transcription from the medical notes.
Qualitative interviews	Interviews will be recorded and transcribed clean verbatim for analysis. The recording is the source.
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 participant expressed a wish to withdraw, the conversation must be recorded in the source data.

10.2 Case Report Form Completion

Where possible, outcome data will be extracted from participant's medical notes and laboratory reports, to complete the **CALIBRE** trial paper CRFs (**Table 6**).

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.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The **CALIBRE** Trial Signature & Delegation Log will identify all those personnel with responsibilities for data collection.

The CRFs will comprise (but will NOT be limited to) the forms in Table 6:

Table 6: CALIBRE Trial CRFs

Form Name
Randomisation Form
Baseline Form
Four Weeks Follow-Up Form (carvedilol arm only)
Six Months Follow-Up Form
12 Months Follow-Up Form
SAE Form
Pregnancy Notification Form
Change of Status Form

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to the **CALIBRE** Work Instruction on CRF completion.

For the **CALIBRE** trial, CRFs will be paper records completed at site, only by those site delegated the task of doing so. 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 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 site's 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 site's PI, or delegate(s), on the CRF.

10.3 Participant Completed Questionnaires

Data collected from the EQ-5D-5L questionnaire forms the basis of one of the secondary outcomes. The questionnaire should generally be completed by the participant alone but physical assistance in completing the form can be given by the research staff where appropriate. In such circumstances questions are to be read to the participant verbatim and responses must not be led by research staff.

Participants should be encouraged to respond to all questions but can refuse to answer any, or all, of the questions should they wish.

Where a questionnaire is returned to the local research staff, in person, with some questions unanswered, research staff should clarify with the participant that they have chosen not to respond specifically to the unanswered questions and that they have not simply missed them in error.

10.4 Data Management

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan. Coding and validation will be agreed between the Trial Manager, Statistician and IT Programmer and the trial database will be signed off once the implementation of these has been assured.

Missing and ambiguous data will be queried using a data clarification system in line with the **CALIBRE** Data Management Plan, and will focus on data required for trial outcome analysis and safety reporting. Single data entry with central monitoring will be employed. **CALIBRE** Trial Office staff at BCTU will transcribe data from completed paper CRFs to an online 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 **CALIBRE** Trial Office staff and will be documented and attributable. 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. There will be no self-evident corrections to data made by the central **CALIBRE** Trial Office staff.

CALIBRE is CTIMP which has been formally risk assessed by BCTU as 'Type A' on the basis that both interventions are already in common usage throughout the UK and the safety profiles are well established. Therefore on-site monitoring will, for the most part, be triggered by poor recruitment or poor data returns. CRFs may be checked against the Source data where on site monitoring is conducted and must be available for verification.

10.5 Data Security

The security of the system is governed by the policies of the University of Birmingham. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the University of Birmingham have to be registered with the Data Protection Officer and data held in accordance with current UK Data Protection Regulations. The University will designate a Data Protection Officer upon registration of the study. The research site has arrangements in place for the secure storage and processing of the study data which comply with the University of Birmingham policies.

The 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 fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls used non-identifiable data etc.
- Network security measures: including site firewalls, antivirus software, and separate secure network protected hosting etc.
- System Management: the System shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.
- System Design: the system shall 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 the Study Centre (University of Birmingham).
- Data processing: Statisticians will have access to anonymised data.
- System Audit: The System shall benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - Periodic IT risk assessments
- Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

10.6 Archiving

All essential documents within the Trial Master File will be archived for up to 25 years after completion of the trial. Electronic data sets will be stored indefinitely.

It is the responsibility of the Principal Investigator at sites to ensure all essential trial documentation and source documents (e.g. signed Informed Consent Forms, Investigator Site Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years.

11. Quality Control and Quality Assurance

Monitoring of **CALIBRE** will ensure compliance with the principles of GCP. A risk proportionate approach to the initiation, management and monitoring of **CALIBRE** has been adopted and outlined in the trial-specific risk assessment.

11.1 Site Set-Up and Initiation

All PIs will be asked to sign the necessary agreements including the **CALIBRE** Trial Protocol Signature page and Delegation log, and supply a current CV and GCP certificate to BCTU. All site staff who are performing trial specific tasks are required to sign the **CALIBRE** Trial Signature and Delegation Log, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a teleconference, at which key members of the 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. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The **CALIBRE** Trial Office must be informed immediately of any change in the site research team.

11.2 Onsite Monitoring

Monitoring is carried out as required following a trial-specific risk assessment and as documented in the Monitoring Plan. Any monitoring activities will be reported to the research team at site and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required the Trial Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow designated BCTU staff access to source documents as requested. The monitoring will be conducted by staff at BCTU.

11.3 Central Monitoring

The Trial Office will be in regular contact with the site research team to check on progress and address any queries that they may have. The Trial Office will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

Sites will be requested to send in copies of signed ICFs and other documentation for in-house review for all participants providing explicit consent. This will be detailed in the Monitoring Plan.

11.4 Audit and Inspections

The PI will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The PI will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

11.5 Notification of Serious Breaches of Good Clinical Practice and/or the Protocol

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial, within seven days of becoming aware of that breach.
For the purposes of this regulation, a "serious breach" is a breach which is likely to effect:

- **The safety or physical or mental integrity of the participants in the trial;**
- **The scientific value of the trial**

Sites are therefore requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trial Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action (CAPA). 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. Any major problems identified during monitoring may be reported to the Trial Management Group, Trial Steering Committee, the REC and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA. A copy is sent to the Sponsor at the time of reporting to the REC and/or relevant regulatory bodies.

12. End of Trial Definition

The end of trial will be nine months after the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The Trial Office will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. If the trial is terminated early, the Trial Office will inform the MHRA and REC within 15 days of the end of trial. The Trial Office will provide them with a summary of the clinical trial report within 12 months of the end of trial. A copy of the End of Trial Notification as well as the summary report will also be sent to the sponsor.

13. Statistical Considerations

13.1 Sample Size

The sample size calculation has been based on published data from both a Cochrane meta-analysis of variceal banding versus beta-blockers [2] and data from the first UK randomised trial of carvedilol published in this disease area [8]. The Cochrane meta-analysis reported an overall 1-year variceal bleeding rate of 12% in the variceal banding ligation group. The 1-year bleeding rate was chosen for the primary outcome as Kaplan-Meier curves suggest that the majority of variceal bleeding occurs in the first year after treatment [8]. In order to detect a 33% proportional difference in variceal bleeding rates (i.e. from 12% to 8%, a 4% absolute difference) between groups using a 2-sided test for comparison of proportions with a 1:1 allocation ratio, 90% power and a type I error rate of 5% (i.e. α=0.05), requires 2362 participants (1181 per group). Assuming and adjusting for a 10% attrition/loss to follow-up rate (based on the similar patient population studied in [8], which is thus a conservative estimate due to our shorter duration of follow-up), increases the required sample size to 2630 participants in total (1315 per group).

13.2 Analysis of Outcome Measures

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

The primary comparison groups will be composed of those randomised to carvedilol versus those randomised to variceal band ligation. All analyses will be based on the intention-to-treat principle, i.e. all participants will be analysed in the group to which they were allocated irrespective of compliance with the randomised allocated treatment or other protocol violation. For all major outcomes, summary statistics and differences between groups (e.g. mean differences, relative risks) will be presented, with 95% confidence intervals and p-values from 2-sided tests also given. Treatment effects will be adjusted for the minimisation variables listed in **section 6.2** where possible. A p-value of <0.05 will be considered statistically significant and there will be no adjustment for multiple testing.

13.3 Primary Outcome Measures

The primary outcome measure of the study is variceal bleeding within the first year after randomisation. This outcome is a binary outcome (i.e. yes/no). The number and percentage of participants experiencing variceal bleeding within 1 year of randomisation will be reported by treatment group. An adjusted relative risk and 95% confidence interval will be estimated from a log-binomial model in order to take into account the minimisation variables listed in **section 6.2.**

The p-value from the associated chi-squared test will be produced and used to determine statistical significance.

13.4 Secondary Outcome Measures

The secondary outcomes for the trial include continuous, categorical and time-to-event data items.

Time to Event Outcomes (e.g. time to first variceal bleed)

Time to event outcomes will be compared between treatment groups using standard survival analysis methods. Kaplan-Meier survival curves will be constructed for visual presentation of time-to-event comparisons. Cox proportional hazard models will be fitted to obtain adjusted treatment effects which will be expressed as hazard ratios with 95% confidence intervals.

Categorical Outcomes (e.g. dysphagia requiring discontinuation of treatment)

For binary secondary outcomes, the number and percentage of participants reporting each outcome will be reported by treatment group. An adjusted relative risk and 95% confidence interval will be estimated from a log-binomial regression model. The p-value from the associated chi-squared test will be produced and used to determine statistical significance.

Continuous Outcomes (EQ-5D-5L)

Continuous outcomes will be reported using means and standard deviations. The EQ-5D-5L will be compared between treatment groups with adjusted mean differences and 95% confidence intervals estimated using linear regression models. Change in EQ-5D-5L score from baseline will also be modelled.

13.5 Planned Subgroup Analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (See **section 6.2**). Subgroup analyses will be limited to the primary outcome. Tests for statistical heterogeneity will be performed prior to any examination of effect estimates within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

13.6 Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all study participants, it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this will include worst-case

assumptions and/or multiple imputation methods. Further sensitivity analyses will include an analysis on the per-protocol population and an unadjusted analysis. Any sensitivity analyses will not, irrespective of their differences, supplant the planned primary analyses. Full details will be included in the SAP.

13.7 Planned Interim Analyses

Interim analyses of major outcome measures and safety data will be conducted and provided in strict confidence to the independent DMEC (see **section 14.5**). Details of the agreed plan will be written in the SAP.

13.8 Planned Final Analyses

The final analysis for the study will occur once all participants have completed the 1-year assessment and the corresponding outcome data have been entered onto the study database and validated as being ready for analysis.

14. Trial Organisational Structure

14.1 Sponsor

The University of Birmingham is the Sponsor for the **CALIBRE** Trial.

14.2 Co-ordinating Centre (CALIBRE Trial Office)

The Birmingham Clinical Trials Unit within the University of Birmingham

14.3 Trial Management Group

The TMG will comprise the CI, other lead investigators (clinical and non-clinical) and members of the BCTU. The TMG will be responsible for the day-to-day running and management of **CALIBRE**. It will convene at regular intervals.

14.4 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will meet at least annually and will monitor trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMEC. Further details of the remit and role of the TSC are available in the TSC Charter.

14.5 DMEC

Data analyses will be supplied in confidence to an independent Data Monitoring and Ethics Committee (DMEC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMEC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMEC will meet at the end of the 12 months internal pilot trial to assess the safety data, as part of the planned interim analysis and advice on continuation to the main trial (see **Section 2.3** for the internal pilot progression criteria). Since this is an internal pilot trial, and these safety data will be included in the main analysis of the **CALIBRE** trial, these data will remain confidential, except to members of the DMEC and the trial statistician(s) performing the analysis.

During the main trial, the DMEC will meet at least annually, or as per a timetable agreed between the DMEC prior to trial commencement. Data analyses will be supplied in confidence to the DMEC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMEC will operate in accordance with the trial specific charter.

If one treatment is substantially better or worse than the other with respect to the primary outcome, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that any one treatment is definitely more, or less, effective than the other. To protect against this, during the main period of recruitment to the trial, interim analyses of the primary outcome and adverse events will be supplied, in strict confidence, to the independent DMEC, along with updates on results of other related studies, and any other analyses that the DMEC may request. The DMEC will advise the chair of the TSC if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt” that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major outcomes, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of other main results. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

14.6 Finance

The National Institute for Health Research (NIHR) Health Technologies Assessment (HTA) Programme is funding this trial (project number: 16/99/02).

15. Ethics Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2017, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and current UK Data Protection Regulations.

This trial will be carried out under a Clinical Trial Authorisation (CTA) in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the REC prior to circulation.

Before any participants are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol participants until written confirmation of R&D approval is received by the Principal Investigator.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments 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 participants.

16. Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with current UK Data Protection Regulations.

Participants will be identified using their unique trial identification number and by the details on the Case Report Form in correspondence between the **CALIBRE** Trial Office. Participants will give their explicit consent for the movement of their consent form, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to BCTU in strict confidence. 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, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for

data transfer (the competent authority and sponsor). Representatives of the **CALIBRE** Trial Office and Sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

17. Financial and Other Competing Interests

The interventions used in **CALIBRE** are already in standard use in the UK and there are no commercial repercussions on using one intervention in preference to another. Members of the TSC and DMEC 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.

18. Insurance and Indemnity

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

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

19. Amendments

All amendments will be tracked in the **CALIBRE** protocol. The decision to amend the protocol and associated trial documentation will be initiated by the TMG. The Sponsor will be responsible for deciding whether an amendment is substantial or non-substantial. Substantive changes will be submitted to REC, HRA, and if required, the MHRA for approval. Once this has been received, R&D departments will be notified of the amendment, and requested to provide local approval.

20. Post-Trial Care

The clinical interventions used in the CALIBRE trial are used in standard care. At the end of the trial follow-up period, the participant's continued treatment will be decided by the clinical care team with reference to current NICE and BSG guidelines.

21. Access to Final Data Set

The **CALIBRE** protocol will be made publicly available via both the **CALIBRE** webpage, hosted by BCTU and subsequently published in an appropriate journal, in advance of the final data set.

The final data set itself will only be available to the direct **CALIBRE** Trial Team, including the TSC, in the first instance. It will also be made available upon formal request when the reason for the request is approved by the TSC.

22. Publication Policy

Regular newsletters will keep collaborators informed of trial progress, and regular meetings will be held to report progress of the trial and to address any problems encountered in the conduct of the trial.

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the CI or delegate and authorship will be determined by the trial publication policy. Participants will be informed of the outcome of the trial via a link to a preview of the publication. A lay summary will also be provided via email or posted to participants prior to publication.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham. Intellectual property rights will be addressed in the Clinical Study Site Agreement or between Sponsor and site.

Appendix 1

International Club of Ascites (ICA-AKI) new definitions for the diagnosis and management of AKI in patients with cirrhosis.[23]

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.**

Appendix 2

Diagnostic criteria of hepatorenal syndrome (HRS) type of acute kidney injury (AKI) in patients with cirrhosis.[23]

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.

Appendix 3

International Club of Ascites grading of ascites.[24]

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.

Appendix 4

West-Haven Criteria for Hepatic Encephalopathy (HE).[25]

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

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