PROTOCOL FULL TITLE:

Beta-blockers Or Placebo for Primary Prophylaxis of oesophageal varices (BOPPP Trial). A blinded, UK multi-centre, clinical effectiveness and cost-effectiveness randomised controlled trial.

Protocol Short Title:

Beta-blockers or placebo for primary prophylaxis (BOPPP) of oesophageal varices trial.

Sponsor:	King's College Hospital NHS Foundation Trust (KCH)
Funder:	NIHR Health Technology Assessment (17/32/04)
Sponsor's protocol number	KCHBOPPP01
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Trial Synopsis

Title of clinical trial	Beta-blockers or placebo for primary prophylaxis of oesophageal varices. A blinded, multi-centre, clinical effectiveness and cost-effectiveness randomised controlled trial.
Protocol Short Title/Acronym	Beta-blockers Or Placebo for Primary Prophylaxis of oesophageal varices *(BOPPP)* Trial
Trial Phase if not mentioned in title	Phase IV
Sponsor name	King's College Hospital NHS Foundation Trust
Chief Investigator	Dr Vishal Patel
Eudract number	2018-002509-78
IRAS number	255446
Medical condition or disease under investigation	Cirrhosis of the liver with small oesophageal varices which have not bled
Purpose of clinical trial	To determine if carvedilol reduces the rate of variceal haemorrhage in patients with cirrhosis and small oesophageal varices
Primary objective	1. To determine the clinical effectiveness of the reduction in variceal haemorrhage in patients treated with carvedilol versus placebo after 3 years. 2. To determine the cost-effectiveness of Carvedilol in patients with small oesophageal varices.
Secondary objective (s)	To determine if primary prophylaxis is cost-effective, and if this therapy can be delivered in primary care
Trial Design	Multi-centre, Phase IV, blinded (participant, investigator, analyst), prospective randomised controlled trial of Beta-blockers Or Placebo for Primary Prophylaxis of oesophageal varices.
Endpoints	*PRIMARY ENDPOINTS* 1. Time to first variceal haemorrhage 2. Cost-utility of NSBB over trial follow up to 3 years. *SECONDARY ENDPOINTS* From baseline to 3 years unless explicitly stated

	1. Estimation of the 1, and 3-year variceal bleed rate by allocation, and associated number needed to treat 2. Progression to medium/large varices requiring clinical intervention 3. Development of gastric, duodenal or ectopic varices 4. Composite of progression in variceal size or variceal bleeding as per 1 and 2 by 3 years 5. Clinical decompensation (spontaneous bacterial peritonitis, new ascites, new hepatic encephalopathy) 6. Progression in Child Pugh grade 7. Progression in MELD score (continuous) 8. Survival (Overall, liver related, cardio-vascular related) 9. Quality of life, EQ-5D-5L
Sample Size	1200 patients
Summary of eligibility criteria	Patients with small (grade 1) oesophageal varices due to cirrhosis of any cause.
IMP, dosage and route of administration	Oral Carvedilol 6.25 mg to 12.5 mg OD. 12.5 mg can be taken as 6.25 mg BD if preferred by patient.
Active comparator product(s)	Oral Placebo 1 to 2 tablets
Duration of trial	Each patient will receive three years of trial medication (Beta Blockers, or Placebo). We anticipate a 24 month (2 year) recruitment phase, and a projected further 39 months (3.25 year) of outcome assessment. BOPPP is a 69 month (5.75 years) trial.
Version and date of final protocol	1.6, 20 NOV 2020

Version Control

Version	Date of version	Reason for change
1.0	20 December 2018	NA - First version
1.1	17 January 2019	1) Updating data collection activity (Healthcare usage questionnaire), 2) Protocolising posting trial IMP if patient loses medication, 3) Harmonising Inclusion Criteria, 4) Updating appendices.
1.2	28 February 2019	1) Phase of clinical trial from III to IV, 2) Modifying Inclusion and Exclusion Criteria, 3) Documenting data collection activities in each visit description, 4) Protocolising that dose modification must be ratified by a clinician
1.3	06 March 2019	1) Inclusion of Patient Identification Centres as trial site type, 2) Naming REC committee, TSC and DMC members
1.4	05 June 2019	1) Version control table inserted, 2) advice about withdrawing patients whose varices progress, 3) tighter definition of inclusion / exclusion criteria, 4) inclusion of data collection activities (text and schedule of visits), 5) advice on endoscopy photo-documentation (text and appendix), 6) inclusion of research nurses for qualitative interviews, 7) tighter rules for IMP dose modification (text and appendix), 8) alert card update for inclusion of IMP dose, 9) statement that 12.5 mg daily dose can be taken as 6.25 mg BD.
1.5	26 February 2020	1) Modified Inclusion Criteria (extended window of OGD diagnosis of Grade 1 varices), 2) inclusion of a new secondary endpoint (gastric, duodenal or ectopic varices), 3) changes to the schedule of visits indicating timeline requirement for pre-consent hepatocellular cancer surveillance ultrasound, 4) advice on adverse event reporting, 5) alert card update for inclusion of date and signing of researcher, 6) clarifications to the qualitative research component, 7) clarified processes on randomisation and 8) inclusion of the MBOP mechanistic sub-study.
1.6	20 November 2020	1) Change in Sponsor contact details. 2) Clarification of exclusion criteria and addition of new criterion. 3) Addition of a repeat staff interview as part of the Qualitative Research. 4) Addition of a COVID-19 guidance section 5) Clarification of withdrawal criteria

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Abbreviations

ACLF	Acute-on-Chronic Liver Failure
AD	Acute Decompensation
ADR	Adverse Drug Reaction
AE	Adverse Event
AKI	Acute Kidney Injury
APRI	Aspartate aminotransferase-to-platelet ratio index
BP	Blood Pressure
BPM	Beats Per Minute
Co-I	Co-Investigator
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CTCAE	Common Technology Criteria for Adverse Events
DMC	Data Monitoring Committee
EC	Ethics Committee
EU	European Union
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FBC	Full Blood Count
GCP	Good Clinical Practice
GI	Gastro-Intestinal
GP	General Practitioner
Hb	Haemoglobin
HCC	Hepatocellular Carcinoma
HE	Hepatic Encephalopathy
HES	Health Episode Statistics
HR	Heart Rate
ICF	Informed Consent Form

ICH	International Conference on Harmonisation
IME	Important Medical Events
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
ITT	Intention to Treat
IV	Intravenous
IVRS	Interactive Voice Response System
KCTU	King's College London Clinical Trials Unit
KHP-CTO	King's Health Partners Clinical Trial Office
MBOP	Mechanism of beta-blockade on bacterial translocation in portal hypertension sub-study.
MHRA	Medicines & Healthcare Regulatory Agency
mmHg	millimetres of mercury
NIHR	National Institute for Health Research
NSBB	Non Selective Beta Blocker
NYHA	New York Heart Association
OD	Once Daily
OGD	Oesophago-gastric duodenoscopy
OLTx	Orthotopic Liver Transplantation
OV	Oesophageal Varices
PIN	Patient Identification Number
PP	Per-Protocol
PO	Per Oral
QoL	Quality of Life
REC	Research Ethics Committee
RN	Research Nurse
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure

SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TE	Transient Elastography
TIPPS	Transjugular Intrahepatic Porto-Systemic Shunt
TS	Trial Statistician
TSC	Trial Steering Committee
TMG	Trial Management Group
UK	United Kingdom
VH	Variceal Haemorrhage
95%CI	95% Confidence Interval

1. Background and Rationale

Liver disease is the fifth commonest cause of death in the developed world and is rising in incidence, with liver failure a common mode of death in these patients[1]. The global disease burden of cirrhosis is rising owing to an increased prevalence of alcohol and non-alcoholic-related liver disease. In England and Wales, it is estimated that 60,000 people have cirrhosis with approximately 11,000 attributable deaths per annum[1]. Standardised mortality has risen by 400% from 1970, commonly in those of working age and in contrast to the other major causes of mortality.

Portal hypertension is a frequent clinical syndrome and complication of cirrhosis that is defined by an increase in porto-systemic pressure gradient in any portion of the portal venous system [2]. Although portal hypertension can result from pre-hepatic portal or splenic vein thrombosis, post-hepatic abnormalities or intrahepatic non-cirrhotic causes; cirrhosis remains the commonest cause of portal hypertension in 90% of cases.

Of the complications that directly result from portal hypertension; the development of varices and variceal haemorrhage (VH) is one of the most significant. The management for varices and variceal haemorrhage has markedly advanced over the past decades due to research on animal models, introduction of new effective treatments and many randomized clinical trials. Through consensus conferences definitions and validated endpoints have been agreed and practice recommendations made. The most recent consensus conference was the 6th Baveno Consensus Workshop 2015[3]. These inform the British Society of Gastroenterology (BSG) guidance [4].

Following the above consensus conferences oesophageal varices (OV) are graded by size or features evident at oesophago-gastric duodenoscopy (OGD) consistent with increased risk of future bleeding (high risk stigmata). Grading of OV is by endoscopic appearance or estimation of diameter (≤5mm is deemed small) and directly affects the risk of VH or death (Appendix 1).

Despite the advances of medical, endoscopic and radiological therapy the mortality rates of acute variceal haemorrhage is still 10%-20% [5]. Prevention of VH is therefore vital in those who have varices.

Prophylaxis against future bleeding can be by pharmacological methods or endoscopic therapies. The main pharmacological choice is non-selective beta-blockade (NSBB) and following several randomised controlled trials of different endoscopic methods band ligation is now the preferred endoscopic therapy of OV. The current evidence base, and international recommendations suggest that there is no benefit of NSBB in pre-primary prophylaxis for patients without varices. However, there is a clear benefit in the reduction of VH with NSBB in patients with moderate-large varices (>5mm in diameter), or those with advanced liver disease[6]. There is currently no clear evidence to guide the use of NSBB in patients with small varices.

The risks of NSBB are that approximately 15% of patients may have absolute or relative contraindications to therapy and another 15% require dose-reduction or discontinuation due to (reversible) side-effects (e.g. fatigue, weakness, shortness of breath) which may discourage patients from using these drugs[10]. In patients with well compensated disease the risk of mortality from NSBB is negligible. There have been concerns on the use of NSBBs in patients with significant decompensation; with an increased risk of death reported in patients with renal impairment, hyponatraemia and refractory ascites [11]. Patients with refractory ascites that are on NSBB for primary prophylaxis should be closely monitored and dose reduction or discontinuation can be considered in those who develop low blood pressure and impairment in renal function[3]. Patients who are well compensated with no or minimal ascites and varices are still likely to benefit from NSBB. While those who have demonstrated intolerance to, or lack of efficacy with propranolol or other older agents may be switched to carvedilol [12].

Of the many NSBB used in clinical practice carvedilol has gained in favour over propranolol or other agents due to its dosing schedule, tolerability and clinical effectiveness. While evidence is clarifying on the best method of primary prophylaxis in large varices [7] there is equipoise on whether those with small varices require primary prophylaxis at all. The implication for this project is that there is sufficient doubt to allow placebo as a control arm in comparisons of NSBB for primary prophylaxis in those with small varices and that carvedilol is an appropriate single agent to investigate.

The main benefits of NSBB include reduction in rate of progression to bleeding or progression to larger varices when initial variceal size is moderate[6] or more. This trial seeks to determine if there is a benefit for those with small varices. NSBBs are low cost, easy to administer and do not require specific expertise (they can be managed in primary care). As they act by decreasing portal pressure, NSBB may also reduce the development of ascites and decompensation [8,9]. Also, once a patient is on NSBB there may be no need for repeat OGD.

Within the trial two ethical issues require further description:

1.1 Progression without meeting the primary outcome

The primary outcome is variceal haemorrhage for which the treatment is band ligation and NSBB. Therefore, if the patient has a variceal haemorrhage they should discontinue IMP, and should be started on NSBB as per clinical standard of care. Similarly, if during surveillance (planned or unplanned), the patient's varices have progressed to medium/large then they also require band ligation and/or NSBB and they should withdraw from the trial and be offered SOC. Participants may be unblinded. This has been explicitly added to the trial design in terms of an important combined secondary outcome, and the power calculation takes this point into account.

1.2 Outcomes following last patient trial visit (at 36 months)

To answer the trial question in an ethical, pragmatic and cost-effective manner we have set follow up at 3 years in terms of trial visits and taking the IMP. Thereafter we would seek permission to glean further information on certain outcomes after the patients' last visit (e.g. at 36 months); i.e. bleeding; progression; mortality; health care utilisation as part of a post IMP follow up period. This will increase the power of the trial and give important further weight to the findings without unduly impacting on the trial budget or burden to the patient. Future access to patient records will be explicitly requested from patients at the time of consent. This will give a *de facto* median follow up of 4 years for the primary outcome, at the end of the study.

2. Trial Objectives and Design

2.1. Trial objectives

Our aim is to determine the clinical and cost-effectiveness in using NSBB in patients with small varices in the primary prophylaxis of variceal bleeding.

Primary objectives

1. To determine the clinical effectiveness of the reduction in variceal haemorrhage in patients treated with carvedilol versus placebo at 3 years.
2. To determine the cost-effectiveness of Carvedilol in patients with small oesophageal varices.

Secondary objectives

1. At 1-year after participant recruitment opens, to assess feasibility of: recruitment, retention acceptability, with progression criteria outlined in internal pilot 1.
2. At 2.5-years, to estimate the control arm 1-year variceal bleed rate, with progression criteria outlined in internal pilot 2.
3. To determine additional clinical benefits of Carvedilol versus placebo for: reduction of variceal size progression, need to initiate endoscopic management of varices (endoscopic band ligation (EBL)), deterioration in liver function (assessed by MELD score and Child-Pugh grade) and all-cause mortality.
4. To investigate how this is best delivered in primary care, by general practice, using qualitative approaches and GP interviews to examine barriers and enablers to implementation.

2.2. Trial endpoints

Primary endpoints

1. Time to first variceal haemorrhage (as defined by Baveno IV criteria[14]).
2. Cost-utility of NSBB over trial follow-up to 3 years.

Definition of variceal haemorrhage

- haematemesis and/or melaena 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

Secondary & tertiary endpoints

1. Estimation of the 1, and 3-year variceal bleed rate by allocation, and associated number needed to treat.
2. Progression to medium/large oesophageal varices at gastroscopy requiring clinical intervention.
3. Development of gastric, duodenal or ectopic varices in the upper GI tract at gastroscopy
4. Composite of progression in variceal size and bleeding as per 1 and 2 by 3 years.
5. Survival (Overall, liver-related, cardiovascular-related).
6. Quality of life, EQ-5D-5L.
7. Decompensation as evidenced by one or more of the following:
    - Spontaneous bacterial peritonitis (ascitic fluid cell PMN cell count >250/mm^3).
    - New hepatic encephalopathy (Defined by West-Haven Grade >1 (overt HE)).
    - New or worsening ascites defined by clinical examination or ultrasound.
8. Progression in Child Pugh grade.
9. Progression in MELD score.

All of the above will be analysed until 3 years from baseline. We will seek permission for collection of primary outcome and Health Episode Statistic (HES) data post cessation of IMP until trial completion.

2.3. Trial design

A UK wide, multicentre, Phase IV, blinded (participant, outcome assessor, investigator, chief investigators, and senior statistician), randomised controlled trial of beta blockade with

Carvedilol versus Placebo in patients with cirrhosis and small varices without evidence of previous bleeding in England, Wales, Scotland and Northern Ireland.

This trial will incorporate both a clinical primary outcome and cost effectiveness outcome to evaluate the benefit to patients and society for earlier intervention with beta-blockers. The clinical primary endpoint is variceal haemorrhage from baseline until 3 years (with further data collection until last patient last visit).

Diagnostic upper GI endoscopy will be performed as per UK 2015 guidelines (4) in that patients will have an annual surveillance OGD. Treatment for VH will be by endoscopic criteria and will not be guided by the trial as this represents an endpoint.

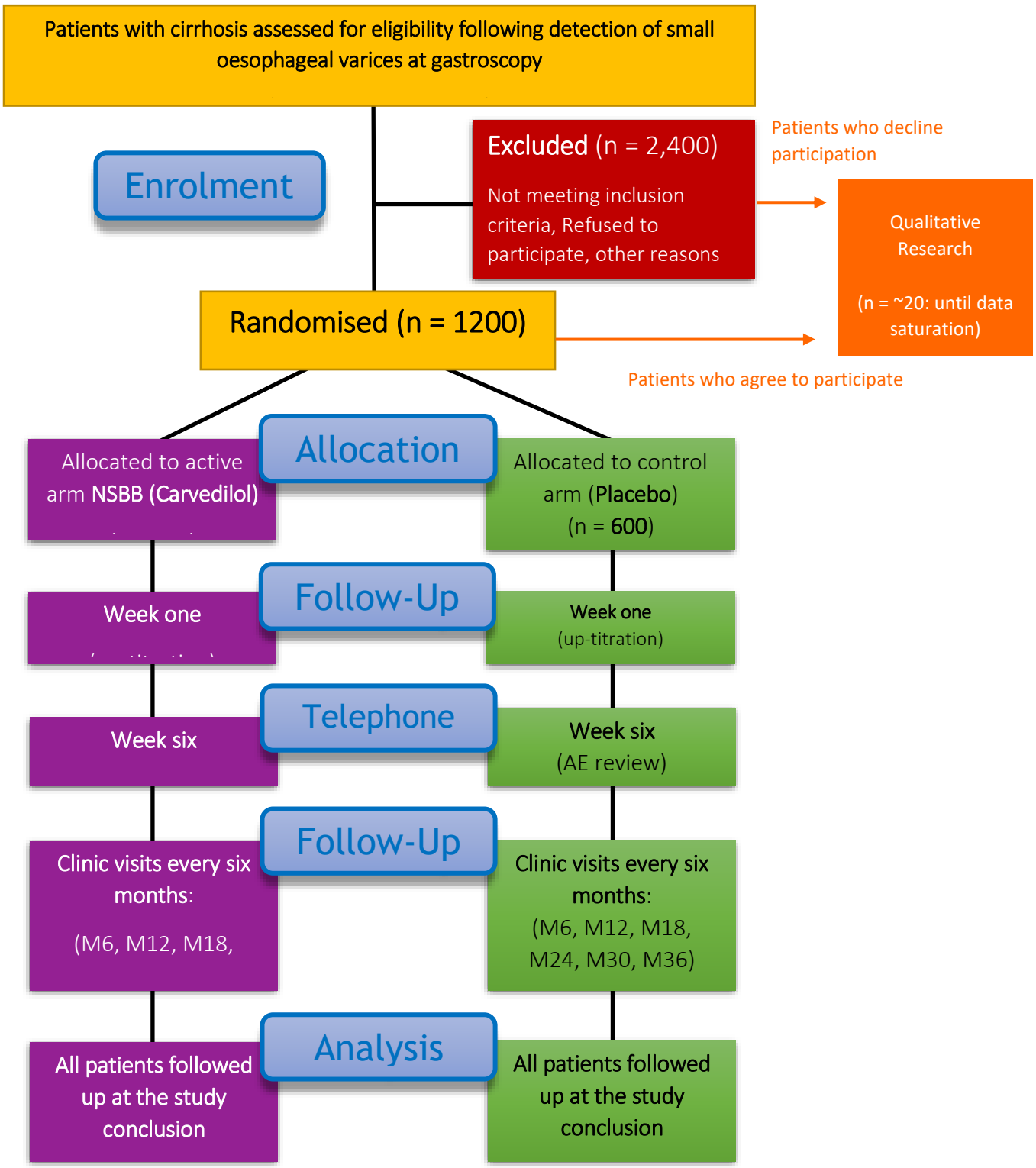
BOPPP includes a qualitative research programme that is part of the main Trial. Patients who are approached for trial participation will also be invited to take part in a one off interview to understand barriers and enablers of trial recruitment. Patients who have consented into the Trial and those who have declined will be interviewed. In addition, research nurses, endoscopists, pharmacists and general practitioners will be interviewed to provide their perspectives on recruitment and Trial intervention implementation.

2.3.1. MBOP

Mechanism of beta-blockade on bacterial translocation in portal hypertension (MBOP) sub-study.

An isolated basic science mechanistic study has been established to investigate the mechanism of effect of Carvedilol in preventing decompensation in patients with cirrhosis. Selected BOPPP sites with -80^{o}C freezer facilities will be offered the opportunity to participate in MBOP, were BOPPP participants will be separately consented to provide biological samples. King's College Hospital will be the sole site until wider funding is obtained to open additional sites. Sites who would be interested should email kch-tr.boppptrial@nhs.net for the MBOP study protocol and appropriate documentation. As MBOP is a sub-study, this study is neither funded nor regulated by the NIHR. There is an MBOP summary in Appendix 9.

2.4. Trial flowchart / Overview



2.5. Schedule of visits

Trial procedures	Pre-screening	Screening Visit	Baseline	Week 1 (+/-) 3 days	Week 6 (+/-) 2 weeks	Month 6 (+/-) 6 weeks	Month 12 (+/-) 6 weeks	Month 18 (+/-) 6 weeks	Month 24 (+/-) 6 weeks	Month 30 (+/-) 6 weeks	Month 36 (+/-) 6 weeks	At variceal bleed	At trial completion (via notes)
Informed consent		X											
Eligibility criteria		X	X										
Randomisation			X										
Demographics*		X											
Medical History*		X											
Targeted physical exam*		X	X***			X	X	X	X	X	X		
Weight / Height*		X	X***			X	X	X	X	X	X		
Vital signs (BP/HR)*		X	X	X		X	X	X	X	X	X	X	
TE/APRI*	X												
FBC, INR, Liver, Renal and Bone profile*			X†			X	X	X	X	X	X	X	
Liver prognostic scores* ɣ			X†			X	X	X	X	X	X	X	
AUDIT-C/alcohol questionnaire*			X			X	X	X	X	X	X		
Variceal Haemorrhage Status						X	X	X	X	X	X	X	
IMP dispensing			Xα			X	X	X	X	X			
Commence IMP			X										
Dose - titration				X	X	X	X	X	X	X	X	X	
HCC surveillance US*	X‡‡					X	X	X	X	X	X	(X)	
Gastroscopy*	X‡‡						X		X		X	X	
Conmeds*			X	X	X	X	X	X	X	X	X		
Adverse Events**				X	X	X	X	X	X	X	X		X
QoL questionnaire			X			X	X	X	X	X	X		
Health Care Usage			X			X	X	X	X	X	X		X
Adherence to IMP				X		X	X	X	X	X	X	X	
Nurse telephone call					X								

Note * standard of care ; ** adverse events collected 30-**day post** completion of treatment, *** not repeated if screening and baseline are within 2 weeks, ‡‡ completed within 6 months of screening (or last SOC surveillance for HSS-US [alternative imaging methods [CT and / or MRI] are permitted as long as the data needed on the source data worksheet is provided]), † completed within 6 months of baseline, ɣ Child-Pugh, MELD, UKELD, CLIF-C AD, α IMP to be allocated within 4 weeks of consent

3. Trial Medication

Procurement, manufacture, packaging and distribution of trial medication has been contracted to MODEPHARMA. The company will provide central distribution services throughout the life cycle of the trial. MODEPHARMA will arrange the sourcing and purchase of commercially available Carvedilol tablets, Placebo manufacture, randomised double-blind IMP packaging, final QP release, storage and distribution of the investigational medicinal products (IMPs). The IMPs will be shipped directly from the final QP releasing site to the trial sites following site initiation. Please refer to the Summary of Product Characteristics and Investigational Medicinal Product Dossier (IMPD) for more details about the active and placebo IMPs.

3.1. Investigation Medicinal Product – active drug

The Investigational Medicinal Product used in this trial is oral Carvedilol. Carvedilol 6.25 mg is presented as an oval, slightly bi-convex white tablet marked S2 on one side and scored on the reverse.

Carvedilol is a vasodilatory non-selective beta-blocker, which reduces heart rate via beta-adrenergic blockade, and reduces peripheral vascular resistance by selective alpha-1 receptor blockade and suppression of the renin-angiotensin system through non-selective beta-blockade. Indications for use include essential hypertension; chronic stable angina pectoris and as an adjunctive treatment in moderate to severe stable heart failure.

For the management of essential hypertension; the recommended initial dose is 12.5 mg once daily; to be up-titrated to a maximum of 50 mg once daily if well tolerated4. In patients with cirrhosis the maximally tolerated dose is expected to be 12.5 mg OD. UK guidance suggests starting carvedilol at 6.25 mg OD and then increasing to 12.5 mg OD (aiming for a target heart rate of 50-55 bpm) is optimal for reduction in portal pressure without increasing the risk of complications of systemic arterial hypotension. The 12.5 mg daily dose can be taken as 6.25 mg BD if preferred by the participant.

To explore if dose escalation can be managed in primary care we incorporate a dose escalation visit at week 1 post randomisation with a trial research nurse, followed by a week 6 telephone call and then revert to 6 month follow up. The early visits provide an opportunity

for safe dose adjustment. We envisage dose escalation to eventually be managed in primary care after the trial is completed.

3.2. Investigation Medicinal Product – placebo

To maintain blinding, high quality placebo tablets will be utilised to provide a complete match with regards to the appearance (e.g. dimensions, markings, colour) of the Carvedilol 6.25 mg tablets being used. The placebo tablets are presented as oval, slightly bi-convex white tablets marked S2 on one side and scored on the reverse. This is the same as the active medication. The 12.5 mg daily dose can be taken as 6.25 mg BD if preferred by the participant.

3.3. Dosing regimen

The two treatment arms will be Carvedilol or Placebo. The IMP will be started at a dose of 6.25 mg OD and up-titrated to a maximum daily dose of 12.5 mg if required at 1-week post-trial start. Following this, the trial drug will be dispensed 6 monthly for a total period of 3 years.

Where required the dose will be up- or down- titrated at clinician discretion, at trial visits and if the patient contacts the trial team regarding side effects. The indication for dose adjustments will be experience of known drug related adverse events; recorded using Common Toxicology Criteria for Adverse Events (CTCAE) version 5.0 (see below). This method is intended to maximise clinical benefit with appropriate up titration.
(https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

In order to achieve the optimal therapeutic benefit from beta-blockade the dose should be escalated after 7 days. We are aiming for at least a 25% reduction in baseline HR and ideally a HR between 50 and 55 bpm. 12.5 mg will be the maximum and target dose used in this trial. Dose modifications with these haemodynamic parameters will be performed by research nurses without direct involvement of BOPPP investigators. The criteria for dose modification is listed in Appendix 2.

Carvedilol is well tolerated, and we expect a low rate of compliance problems or requirement for discontinuation due to adverse events (AEs). However, to capture any AEs following up titration a telephone call from a research nurse is planned at 6 weeks. There will be an opportunity to discuss dose reduction at this stage. This is intended to improve compliance. The maximum dose in this trial is chosen to reflect experience and current practice in patients with medium to large varices who receive carvedilol.

Criteria for a pause in beta-blocker therapy:

- Systolic blood pressure < 90mmHg
- Spontaneous bacterial peritonitis
- Acute kidney injury
- Hyponatraemia (Na < 125 mmol/L)
- Sepsis / GI Bleeding
- To facilitate cardiac stress testing

Once the reason for stopping Carvedilol has resolved the IMP should be re-instituted at the previously tolerated dose

Criteria for permanent discontinuation in beta-blocker therapy:

- Red Flag symptoms (CTCAE grade 3 chest pain or syncope)

3.4. IMP risks

Section 4.8 of the Summary of Product Characteristics (SmPC) for Carvedilol 6.25 mg will act as the reference safety information. A summary of the contraindications to beta blocker use are described within section 4.2 (Exclusion Criteria).

3.5. Drug accountability

Trial specific stock will be distributed to each site following the final QP release, once all regulatory and local approvals are in place. The pharmacy clinical trials team must maintain

accurate accountability records of the IMP, including, but not limited to, the number of bottles/tablets received, the number of bottles/tablets dispensed to which participant, batch number, expiry date, and quantity of investigational medicinal product returned by the participant.

Participants will be asked to return any unused IMP and/or empty packaging at each visit. This is to allow the research team to check compliance and for accountability purposes. All study drug returns must be returned to pharmacy for reconciliation on the Investigational Product Accountability Log. Study drug returns will be verified by the trial clinical research associate (CRA) prior to disposal at site. Destruction of IMP must be in accordance with the site IMP destruction SOP. Records of IMP destruction and related correspondence must be filed in the relevant section of the pharmacy trial file.

3.6. Packing and storage of IMP

All active and placebo tablets will be packed in labelled HDPE bottles with a child-security lid and a tamper-evident seal. Each HDPE bottle will contain 210 active or placebo tablets. This is sufficient for 15 weeks (2 tablets per day) as well as for 6 months (1 tablet a day). The IMP must be stored in its original packaging. There are no special storage conditions. Store at ambient room temperature, but not above 30^{oC}.

3.6.1. Trial medication labelling

All bottles have an Annex 13 compliant clinical trial label with a unique pack number printed on it. All drugs will be dispensed by the Pharmacy Department against a trial specific prescription. Upon dispensing the site pharmacy team will hand-write the patient identification number (PIN) and the name and site of the Principal Investigator on the existing label in the field provided. The information presented on the labels for the IMP will comply with applicable national and local regulations.

3.6.2. Transportation of trial medication to hospital Pharmacy

MODEPHARMA will arrange the distribution of the trial medication to each site via approved medical supplies courier. Resupply will be arranged with the distributor, through the King's Clinical Trials Unit (KCTU) trials pharmacist (after approval to ship IMP has been received from the Chief Investigator). Medication will usually reach site within 1-2 days of receiving confirmation to ship. The Trial Manager is responsible for notifying the trials pharmacist of rates of recruitment, patient withdrawals and patients in screening to ensure enough IMP is stocked at sites. The procedure for ordering IMP will be in the pharmacy manual. Should a trial participant lose their trial medication and they cannot attend the hospital, arrangements will be made to post replacement IMP to the participant by following a trial specific operating procedure.

3.7. Trial participant compliance

Treatment compliance will be assessed by means of a pill count undertaken by the research nurse at each protocolled research visit. Compliance data and pill counts will be recorded in the CRF and will form part of monitoring by the CRA. Patients will be recorded as having complied to taking the trial medication if at least 50% of the number of pills that should have been removed, were removed i.e. less than 50% of the trial IMP tables have been returned. Situations where patients have returned more than 50% of the trial IMP must be recorded as a protocol deviation. Refer to the supporting trial information for reporting to the BOPPP trial team.

3.8. *Concomitant medication*

Carvedilol is a substrate as well as an inhibitor of P-glycoprotein. Therefore, the bioavailability of drugs transported by P-glycoprotein may be increased with concomitant administration of carvedilol. In addition, the bioavailability of Carvedilol can be modified by inducers or inhibitors of P-glycoprotein. Inhibitors as well as inducers of CYP2D6 and CYP2C9 can modify the systemic and/or pre-systemic metabolism of Carvedilol stereo-selectively, leading to increased or decreased plasma concentrations of R and S-Carvedilol. Patients receiving

medicines that induce (e.g. rifampicin, carbamazepine and barbiturates) or inhibit (e.g. paroxetine, fluoxetine, quinidine, cinacalcet, bupropion, amiodarone and fluconazole) these CYP enzymes must be monitored closely during concomitant treatment with Carvedilol.

Additionally, there may be other pharmaco-dynamic interactions with other drugs (beta-blockers, calcium channel blockers, anti-arrhythmic agents and antihypertensive agents). Careful monitoring will be undertaken with concomitant medications that have a potential documented action with Carvedilol.

Patients that require beta-blockade for portal hypertensive or non-portal hypertensive reasons, or who requires medication with significant interactions with beta-blockers (such as rate limiting calcium channel antagonists), will have the trial IMP discontinued permanently if the need will be lifelong. After a one-week washout period, the patient can be started on the relevant medication. Starting medication(s) with significant interactions earlier than advised will be at the treating clinicians' discretion and must be recorded in the patients' medical notes and the CRF. Similarly, patients should stop a beta-blocker or relevant medication(s) with known significant interactions prior to enrolment in BOPPP for at least 1-week prior to initiation of IMP.

The BOPPP trial team will inform the patients' GP if they require beta-blockade for cardiovascular or liver related reasons. We will continue to collect data with the patient's consent following the cessation of trial IMP, unless they fully withdraw consent from BOPPP.

For management of concomitant therapies, please refer to the Carvedilol Summary of Product Characteristics. A complete listing of all concomitant medications being taken by the patient will be recorded in the CRF at each visit. All routine concomitant medication will be allowed during the trial with the exception of anti-arrhythmic medications with significant interactions with beta-blockers, but the only beta-blocker administration allowed will be as specified in this protocol.

4. Selection and Withdrawal of Participants

4.1. Inclusion criteria

- Age 18 years and over
- Cirrhosis and portal hypertension, defined by any 2 of the following:
  - Characteristic clinical examination findings; one or more of
    - Characteristic liver function tests
    - Haematological panel
    - Coagulation profile abnormalities
  - Characteristic radiological findings; one or more of
    - Heterogeneous liver with irregular contour
    - splenomegaly
    - ascites
    - varices
    - recanalized umbilical vein
  - FibroScan liver stiffness measurement >15 kPa without other explanation
  - Fibrosis score > stage 4 on liver biopsy (presence of a relevant fibrosis score by biopsy does not require additional clinical examination / radiological / FibroScan supporting evidence)
- Small oesophageal varices diagnosed within the last 6 months, defined as ≤5 mm in diameter or varices which completely disappear on moderate insufflation at gastroscopy.
- Not received a beta-blocker in the last week
- Capacity to provide informed consent

4.2. Exclusion criteria

- Non-cirrhotic portal hypertension
- Current medium/large oesophageal varices (defined as >5 mm in diameter)
- Previous medium/large oesophageal varices (defined as >5 mm in diameter), which decreased in size with curative therapy
- Gastric (IGV and GOV2), duodenal, rectal or other ectopic varices with or without evidence of recent bleeding. For gastric varices, this includes:

1. IGV-1 and IGV-2 (isolated gastric varices)
2. GOV2 (gastric varices continuing into the cardia)
3. *Note GOV1 (gastric varices continuing into the lesser curve) are not an exclusion if present with small oesophageal varices*

- Previous variceal haemorrhage
- Previous band ligation or glue injection of oesophageal and/or gastric varices
- Red signs accompanying varices at endoscopy
- Known intolerance to beta blockers
- Contraindications to beta blocker use:
  - Heart rate <50 bpm
  - Known 2nd degree or higher heart block
  - Sick sinus syndrome
  - Systolic blood pressure <85 mmHg
  - Chronic airways obstruction (asthma/COPD)
  - Floppy Iris Syndrome
  - CYP2D6 Poor Metaboliser
  - History of cardiogenic shock
  - History of severe hypersensitivity reaction to beta-blockers
  - Untreated phaeochromocytoma
  - Severe peripheral vascular disease
  - Prinzmetal angina
  - NYHA IV heart failure
- Unable to provide informed consent
- Child Pugh C cirrhosis
- Already receiving a beta-blocker for another reason that cannot be discontinued
- Graft cirrhosis post liver transplantation
- Evidence of active malignancy without curative therapy planned
- Pregnant or lactating women
- Women of child bearing potential not willing to use adequate contraception during the period of IMP dosing
- Patients who have been on a CTIMP within the previous 3 months
- Clinical symptoms consistent with COVID-19 (a high temperature, a new continuous cough or a loss or change to sense of smell or taste) at the time of randomisation

Special considerations

Asthma – sites are encouraged to investigate the true burden of asthma. Symptomatic patients with a dependency of inhalers are clearly contraindicated to Carvedilol and ineligible for BOPPP. However, when a patient has a historical diagnosis and is not symptomatic and / or not dependent on steroidal / preventative inhalers: then the diagnosis should be challenged and discussed with the patient and their GP. If the latter suggests that the patient is not asthmatic according to British Thoracic Society (BTS) guidelines, correction of the patient's asthma diagnosis should be considered and documented in the patients' medical notes before being consented for participation in BOPPP.

4.3. Selection of participants

Patients at risk of developing OV are reviewed 6 monthly as per standard of care protocols with surveillance endoscopy undertaken annually. Participants will be identified from secondary or tertiary hospital services following screening or surveillance endoscopy standard of care procedures, or during routine follow up for the management of cirrhosis. Patients can be identified from Patient Identification Centres (PICs) and referred to recruiting sites. Photo-documentation will be required to verify the grade of OV in order to confirm participant eligibility. Reports from liver ultrasound scans for hepatocellular carcinoma (HCC) surveillance should be performed within 6 months of screening, or the last standard of care interval, and retained for each participant. Alternate imaging methods (e.g. MRI or CT) are permissible as long as the necessary data can be collected i.e. hepatomegaly (Y/N, splenomegaly (Y/N), spleen size (cm), hepatic vein patent (Y/N), portal vein patent (Y/N), radiological ascites (Y/N), focal liver lesions (Y/N).

Local clinical care teams will be key in assisting to identify these patients during their review / pre-screening of endoscopy and clinical records. As part of the qualitative research within the trial, we will analyse potential eligible patients' reasons for declining participation. Patients who decline to enter the trial will be offered the opportunity to participate in a qualitative interview aimed at understanding the motivation for non-participation. A summary of the recruitment process is shown in below Figure 2.

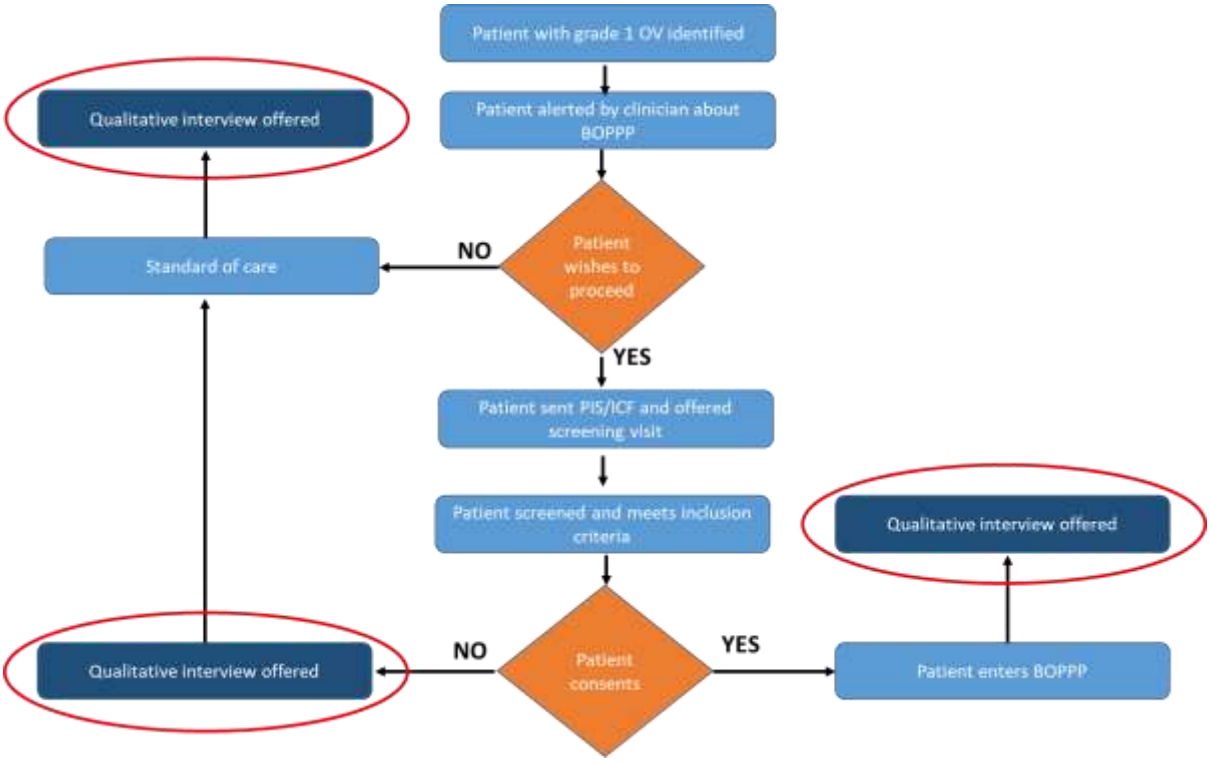


Figure 2: Screening and informed consent Note: Qualitative research offered to patients that have been approached for BOPPP participation.

4.4. Permanent withdrawal from trial drug

Participants have the right to permanently withdraw from taking trial drug at any time. Temporary cessation is discussed in section 3.3 and appendix 2. The investigator also has the right to withdraw patients from the trial drug in the event of inter-current illness, AEs, SAEs or SUSARs. Among others, the following criteria are definite reasons for withdrawal – pregnancy, requirement for beta-blockade (e.g. variceal haemorrhage, or following cardiac or cerebrovascular event) and withdrawal of patient consent to treatment.

Should a patient or treating clinician decide that permanent withdrawal from trial drug is necessary; all efforts will be made to report the reason for withdrawal in as much detail as possible. In the absence of withdrawal of consent for follow-up, these patients should continue with follow-up as per the trial schedule and efforts will be made to obtain safety and endpoint data. If the patient discontinues the IMP before the full 3-year trial period, they will be followed-up until last patient last visit provided he/she does not withdraw consent.

We will continue to collect lab parameters, QoL, healthcare utilisation data and AUDIT-C / alcohol consumption data during the follow-up period even if the IMP has been discontinued and will seek consent for this.

If participants experience events that represent progression and meeting a secondary endpoint, they should be permanently withdrawn from trial IMP, may be unblinded and SOC provided, which may include commencement of NSBB and/or offering endoscopic band ligation of oesophageal varices. These events include:

1. have a variceal haemorrhage
2. oesophageal varices increase in size to grade II and/or grade III
3. development of gastric, duodenal or ectopic varices in the upper GI tract at gastroscopy

SOC may also include consideration for other appropriate clinical trials depending on participant choice. Participants will not be expected to attend trial visits but healthcare usage and mortality will be checked at the End of Trial.
If a patient subsequently undergoes a Transjugular Intrahepatic Porto-Systemic Shunt (TIPPS) or orthotopic liver transplantation (OLTx), they should have IMP discontinued and they can be withdrawn from further follow-up but data will be collected at the end of the trial via HES.

4.5. Permanent withdrawal from the trial

Participants have the right to withdraw from the trial at any time for any reason. The investigator also has the right to withdraw participants from the trial drug in the event of inter-current illness, AEs, SAEs, SUSARs, repeated protocol deviations / violations, cure, or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the trial un-interpretable; therefore, unnecessary withdrawal of participants should be avoided. Should a participant decide to withdraw from the trial, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a participant withdraw from trial drug only, efforts will be made to continue to obtain follow-up data, with the permission of the patient. The withdrawal rate will be reported routinely to the Data Monitoring Committee.

4.6. Expected duration of trial

The trial will recruit patients over a period of 2 years with follow up of the last patient (i.e. minimum follow up) expected to be for 3 years. End of trial is defined as date of database lock.

5. Trial Procedures and Visits

Trial interventions will be undertaken as outlined below and in accordance to the schedule of activities in Figure 2. Visits were purposefully scheduled to match standard of care practice visits and procedures. Research only visits include screening, baseline and week 1 visits.

5.1. Setting and context

Patients will be recruited from secondary or tertiary (hospital) services (following screening or surveillance endoscopy) when undergoing standard of care (SOC) procedures or visit for the management of cirrhosis. Principal investigators identified at all centres are active proponents of clinical research; and all centres identified have an active research portfolio, integrating research activity with clinical care. This has been identified as crucial to this project as the trial interventions are for the most part reflective of standard of care treatment.

5.2. Identifying patients

Pre-screening of clinic records will be undertaken by the local clinical care teams to identify suitable patients for the trial. This includes standard of care gastroscopy results, transient elastography (TE, if available), aspartate aminotransferase-to-platelet ratio index (APRI) and an assessment of hepatocellular carcinoma (HCC using US, CT and/ or MRI). Endoscopy reports will require as a minimum the following information and must be available in the participants' source document folder:

- Size of oesophageal varices based on grading criteria
- Number of columns of oesophageal varices

- Any red signs present affecting oesophageal varices
- Presence of gastric varices (GOV1, GOV2, IGV1, IGV2)
- Any red signs present affecting gastric varices
- Presence of duodenal varices

It is recommended that photo-documentation of standard landmarks on endoscopy reports is undertaken as per current UK guidelines to confirm the details of the endoscopists' report (see Appendix 1):

- Lower oesophagus (note current European guidelines advice on photographing the upper oesophagus, but this is not optimal for capturing appearances of oesophageal varices)
- Gastro-oesophageal junction
- Body of stomach
- Gastric antrum
- Fundus in retroflexion
- Incisura in retroflexion
- Duodenal bulb
- Distal duodenum

In addition, it is important to photo-document the lower oesophagus to demonstrate that small varices are present, with and without air insufflation. It is recommended that two photographs are captured as follows:

1) Lower oesophagus demonstrating small varices present, without air insufflation
2) Lower oesophagus demonstrating small varices collapsed with air insufflation

The treating clinician will obtain verbal consent for the patient to be contacted by the research team; via telephone or email, as per patient preference. This will be documented in the patient records. The BOPPP trial participant information sheet (PIS) will be supplied to those in agreement and a follow up screening appointment arranged. At all times, the patient will have the opportunity to read the PIS and ask any questions regarding the conduct of the trial. There is no minimum period to be adhered to between receiving the PIS and a screening appointment.

5.3. Screening visit and informed consent

During the screening visit, the research team will confirm with the patient that they have had the opportunity to read and understood the PIS and will discuss with the patient allowing them to ask any questions regarding the conduct of the trial. The risks and benefits that are outlined in the PIS will be discussed at the screening visit so that patients assessed to be fully informed. Written informed consent will be obtained using the BOPPP trial informed consent form (ICF) and full eligibility will be determined by a member of the local research team (e.g. research nurse), with verification by the Principal Investigator. The patients will then be entered into BOPPP. The ICF will be signed off by the PI or delegated clinician. Assessments include demographic data collection, clinical review of medical history, targets physical exam, weight / height and vital signs. Of note: re-screening of patients who previously did not meet eligibility criteria is allowed as the variceal status may vary as part of the natural history of cirrhosis.

Once the patient has agreed or declined to participate in BOPPP, they will be given a qualitative research PIS and asked if they are happy to be contacted by the qualitative researcher to discuss taking part in a 20-30 minute telephone conversation/face-to-face interview about why they have or have not decided to take part in the trial. If patients consent, they will be asked for their contact details to be provided to the qualitative researcher who will answer any questions they might have and if take informed consent to participate. See sections 5.4.2 and 5.10 for more details.

5.4. Baseline visit

The baseline visit will involve:

- deprivation assessment
- targeted physical exam, including grading of ascites and hepatic encephalopathy, Glasgow Coma Scale assessment, weight/height, vital signs (blood pressure, heart rate)
- Blood tests: full blood count (FBC), international harmonised ratio (INR), liver profile, renal and bone profile, as part of standard of care procedures. Blood test parameters are specified in the source document worksheets. If the baseline visit occurs outside

the standard of care window, the trial sites can utilise the most recent standard of care blood test results if the following apply:

- they have been taken within the last 6 months
- the patient is deemed to be stable, so the results are reflective of the patient's current health status and would be considered reliable for clinical decisions to be made based on these.

In all cases, the situation must be communicated to the central trial team for assessment by the Trial Statistician.

- Disease severity and prognostic score calculation: Child Pugh, MELD, UKELD and CLIF-C-AD
- Baseline QoL, healthcare resource questionnaire and AUDIT-C questionnaire will also be completed by the patient

Randomisation is performed at this visit, along with concomitant medication review and start of trial medication. Note (1) – the aforementioned 'Baseline' procedures may occur on the same day as the screening visit if this reduces the burden on the trial participant. Note (2) If the Baseline visit is within two weeks of the screening visit, the Targeted Physical Exam and weight / height are not required at baseline.

5.4.1. Randomisation

Randomisation will be undertaken by the local research team at each site once written informed consent has been obtained, eligibility confirmed and baseline data collected. Randomisation should be completed within 4 weeks of participant consent. Following consent and once the registration page has been completed and saved in the Elsevier EDC MACRO system; each participant will be allocated a unique six-digit Participant Identification Number (PIN). This number will be the sole identifier to be used on the paper source data worksheets and electronic data forms in MACRO. The first two digits of the PIN will indicate the hospital recruitment site number. The last four digits of the PIN will indicate the patient, for example 030015, would denote site 03 and patient 0015. This will be the main participant identifier for those recruited. Once the PIN is obtained, the trial team member will log into a separate secure multiuser multisite online randomisation system developed and managed by

the King's College London Clinical Trial Unit (KCTU). The PIN and some participant identifiers will be submitted into the randomisation system for treatment allocation. The treatment allocation results (blinded) will be emailed to staff with approved user access, including the site pharmacy. No allocation of trial drug is needed at randomisation as this is automatically completed at this time point.

Following randomisation and collection of IMP, patients will be booked to return for the week 1 up titration visit. The allocation sequence of each permuted block will be concealed from participants, clinicians, researchers and analysts.

5.4.2. Qualitative interviews to understand recruitment

As mentioned previously, BOPPP has incorporated a Qualitative Research component into the Protocol to understand the barriers and enablers of trial recruitment at two levels (i) patient level, (ii) research site level. Please see section 5.10. "Qualitative Interviews" for further details.

5.5. Week 1 Visit (dose titration)

A one-week visit will be conducted by research nurses focussed on trial medication up titration. At that visit research nurses will take a routine history for any adverse events experienced since commencement of trial medication. Particular attention will be placed on the following symptoms, as experience of any of these will affect trial drug dose modification: collapse, palpitations, chest pain, rash and erectile dysfunction in males. A focussed set of observations (heart rate and blood pressure) will be taken. Trial drug modifications / dose titration will be done following the criteria outlined in Appendix 2 as well as recording of concomitant medications and pill count.

5.6. Week 6 safety telephone call

At this telephone call, research nurses will take a routine history adverse events; in particular, for collapse, palpitations, chest pain, rash and erectile dysfunction in males. For patients with significant cardiac symptoms (chest pain, multiple collapses) the patient will be advised to go

to the emergency department (ED). For those with palpitations, single collapse, rash or erectile dysfunction the default advice is to seek advice in primary care (GP or NHS Direct on 111).

Hepatological indications to withhold IMP are due to decompensation such as bleeding, sepsis, acute kidney injury (Appendix 3) or spontaneous bacterial peritonitis. Where an indication for NSBB has become apparent (e.g. variceal haemorrhage) the patient should suspend IMP and undergo SOC. Where the indication to stop IMP is temporary (e.g. vasopressor dependent septic shock, spontaneous bacterial peritonitis) this should be recorded and reported to the CTU and TM, and IMP restarted when safe to do so (at the discretion of the local PI). Any decision to stop IMP must be made in consultation with the local PI and reassessed at 1-week post cessation with a view to restart. In patients who stop IMP permanently, outcome data will be collected until trial end and the patient's GP will be informed.

*5.7. Month 6-36 (+/- 6 weeks at each interval) *standard of care follow up procedures**

Participants will receive clinical review in the out-patient setting:

- clinical review of medical history
- deprivation assessment
- targeted physical exam, including grading of ascites and hepatic encephalopathy, Glasgow Coma Scale assessment, weight/height, vital signs (blood pressure, heart rate)
- Blood tests: full blood count (FBC), international harmonised ratio (INR), liver profile, renal and bone profile, as part of standard of care procedures. Blood test parameters are specified in the source document worksheets.
- Disease severity and prognostic score calculation: Child Pugh, MELD, UKELD and CLIF-C-AD
- Baseline QoL and healthcare resource questionnaire will also be completed by the patient
- AUDIT-C questionnaire completed by the patient at months 0, 12, 24 and 36 with limited alcohol consumption questions to be completed at months 6, 18 and 30.

- Variceal haemorrhage status
- Surveillance liver ultrasound for hepatocellular carcinoma (US, CT and / or MRI), as part of standard of care

IMP for the current period will be returned by the patient so adherence can be assessed by pill count at each trial visit and the next 6-month period dispensed. Concomitant medication and adverse events will be recorded with consideration of dose up or down titration. Participants will be asked to complete EQ-5D-5L QoL, healthcare resource questionnaire and AUDIT-C or alcoholic consumption questionnaire. A gastroscopy examination will be undertaken at yearly intervals only.

At the completion of the trial (prior to database lock, this may be almost five years from recruitment for some patients)) variceal bleed, mortality, MI, and liver transplant will be recorded in participants' notes and in the Trial Completion Review form in the EDC.

5.8. End of treatment (of early discontinuation) procedures

Participants who discontinue trial medication before the allocated period can continue within the trial, entering in a follow up only phase. This will involve collection of routine standard of care data and completion of QoL questionnaires. A final assessment will be completed at trial end (last patient last follow up). If a participant indicates their wish to formally withdraw consent for further follow-up in the trial for any reason, this will be honoured and the patient will return to SOC. In any case, if patients have not fully withdrawn all outstanding data should be reported and all queries resolved.

5.9. Extended follow up by electronic record linkage

Participants will be asked to provide consent to be followed up electronically by record linkage to NHS electronic datasets (*e.g.* the Health Episodes Statistics in England and corresponding datasets in Wales / Northern Ireland / Scotland) and to the death registry up to 10 years post randomisation. The aim will be to assess the impact of the period of randomised treatment on long-term outcomes. Failure to provide this separate consent will

not exclude the participant from participating in the trial. This extended follow-up will not be considered a formal component of the main trial.

5.10. Qualitative interviews

5.10.1. Patient level to understand recruitment barriers and enablers

Qualitative interviews will examine the decision-making process among an estimated 20 patients who either agree or decline to participate in the trial. After consent to participate in BOPPP has been obtained or declined, patients will be given a PIS for the qualitative interview and asked for verbal consent to be contacted by the qualitative research assistant who will follow up with a phone call to answer questions and / or schedule one-off appointments. Fully informed consent will be obtained using the informed consent form (ICF) in person or by verbal means, with a witness to verify consent on the ICF. Recruitment for qualitative interviews will continue until data saturation is reached.

Trial participants will be asked for their views on the process of screening, consent, baseline visit and one-week review to identify further barriers to participation including the acceptability of randomisation and other benefits and risks associated with the proposed intervention and trial participation. Interview topic guides will be revised iteratively in response to the priorities and concerns of participants.

Selected participants may be requested to take part in a video interview for the Trial website. The interview will consist of questions regarding their participation in the trial.

5.10.2. Site level to understand recruitment barriers and enablers

An estimated 10 endoscopists (e.g. 5 sites with 2 endoscopists per site) and 10 research nurses across the sites will be contacted via email / phone and invited to participate in a qualitative interview to examine the barriers and challenges to delivering the treatment strategy within trial period and beyond the BOPPP trial within the NHS setting.

Following the pause/re-start of the trial due to COVID-19, staff may be invited to take part in a repeat interview.

Qualitative data at patient and site level will be used within internal pilot 1 to inform the written and verbal organisation of trial information, recruitment procedures and support strategies needed to optimise recruitment and retention.

5.10.3. Interviews with General Practitioners (GPs)

An estimated 20-30 telephone interviews will be conducted with GPs to understand the barriers and enablers to implementation in primary care beyond the trial context in. Interviews will investigate the perceived acceptability, challenges and concerns around dose titration for patients with small oesophageal varices within primary care. The optimal timing of primary care involvement, the role of other primary care professionals, e.g. practice pharmacists, and the information, support and infrastructure required with secondary and tertiary care centres will be examined. Themes identified in GP interviews, and internal pilot interviews with endoscopists, will inform the topic guide used in two subsequent focus groups with local endoscopists, gastroenterologists, GP's, practice pharmacists and nurses that will examine strategies and potential solutions to early dose adjustment as part of routine clinical care.

5.11. Quality of Life and Health Economic Analysis

Quality of Life (QoL) and healthcare resource assessment will be undertaken at baseline, 6,12, 24, 30 and 36 months using the EQ-5D-5L tool and a bespoke healthcare resource questionnaire. The EQ-5D-5L is an existing and validated multi – attribute utility instrument for measuring health related QoL in cost effectiveness analysis. The QoL tool essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level

selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. The number is a used primarily to characterise the response although it can facilitate some comparative analysis directly.

A tariff set is available to score EQ-5D-5L health states based on survey data from the English population[13]. The tariff set provides a quality of life score for each unique response to the EQ-5D-5L. Scores range from 1 to -0.284 where 1 represents full health and 0 represents death. Around 5% of responses to the EQ-5D-5L have an associated tariff which is negative (considered worse than death). The tariffs were generated by a mixture of time trade-off and Discrete Choice Experiment survey data on a subset of the 3125 health states described by the instrument, in combination with regression modelling.

The EQ-5D-5L records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The EQ-5D-5L can be used as a quantitative measure of health outcome that reflects the patient's own judgement.

The healthcare usage assessment encompasses a three-page questionnaire that focuses on the participants' use of 1) residential and respite care, 2) day care and rehabilitation services, 3) community health services and 4) community social services. With both questionnaires, the participant will be asked to complete unaided. The research nurse will review the questionnaires before the participant leaves clinic in order to clarify questions with multiple answers.

5.12. Overview of outcome measures by visit

Outcome measures will be recorded at the time-points defined in the table below (Table 1). If a patient presents with a variceal bleed between assessments, this will be reported of the date presented and outcomes assessed on that day. Interventions that are not current standard of care have been **highlighted in bold**.

At each visit participants will be asked for any evidence of adverse events, or for evidence of primary or secondary outcomes.

Time point	Scheduled activity
Pre - Screening	▪ All patients with cirrhosis and small oesophageal varices identified at surveillance endoscopy will be screened for inclusion in this trial.
Eligibility / Screening	▪ All screened patients will be assessed using the trial inclusion and exclusion criteria. Gastroscopy will be photo-documented
Informed Consent	▪ Patients identified at screening who meet the inclusion and exclusion criteria will be offered the opportunity to take part in the trial. Potential participants will be given education on the risk of varices progression and on the benefits and risks of treatment with the IMP (Carvedilol) from the trial site team, and confirming the possibility of being assigned to placebo arm. ▪ If they agree they will be asked to give written informed consent. ▪ Patients consenting and not consenting for participation in BOPPP will be offered qualitative interview, provided with Qual PIS, and asked for consent to forward contact details to Qual researcher
Baseline	▪ Participants will be randomised to receive either beta-blocker or placebo. ▪ Participants will complete the EQ-5D-5L QoL, Health Care Usage and AUDIT-C questionnaire. ▪ Participants will receive further education on the trial and the IMP and then commence treatment.
Week 1 (+/- 3 days)	▪ Participants will be reviewed to assess adherence and for any adverse events related to the IMP. ▪ Clinical assessment to include measurement of vital signs ▪ If they are tolerating the IMP well and if the heart rate is > 60 bpm and SBP > 100 mmHg then dose of IMP will be increased as per the protocol.
Week 6 (+/- 2 weeks)	▪ Participants will receive a safety telephone review to assess for any adverse events related to the IMP.
Month 6 (+/- 6 weeks)	▪ Participants will receive clinical review in the out-patient setting, laboratory testing and surveillance liver ultrasound. ▪ Participants will complete EQ-5D-5L, Health Care Usage and alcohol consumption questionnaires.
Month 12 (+/- 6 weeks)	▪ Participants will receive clinical review in the out-patient setting, laboratory testing, surveillance liver ultrasound and varices surveillance gastroscopy. ▪ Participants will complete EQ-5D-5L, Health Care Usage and AUDIT-C questionnaires.
Month 18 (+/- 6 weeks)	▪ Participants will receive clinical review in the out-patient setting, laboratory testing and surveillance liver ultrasound. ▪ Participants will complete EQ-5D-5LHealth Care Usage and alcohol consumption questionnaires.
Month 24 (+/- 6 weeks)	▪ Participants will receive clinical review in the out-patient setting, laboratory testing, surveillance liver ultrasound and varices surveillance gastroscopy. ▪ Participants will complete EQ-5D-5L, Health Care Usage and AUDIT-C questionnaires.
Month 30 (+/- 6 weeks)	▪ Participants will receive clinical review in the out-patient setting, laboratory testing and surveillance liver ultrasound. ▪ Participants will complete EQ-5D-5L, Health Care Usage and alcohol consumption questionnaires.
Month 36 (+/- 6 weeks)	▪ Participants will receive clinical review in the out-patient setting, laboratory testing, surveillance liver ultrasound and varices surveillance gastroscopy. ▪ Participants will complete EQ-5D-5L, Health Care Usage and AUDIT-C questionnaires.

Table 1. Trial visits and assessment of efficacy and safety.

5.13. COVID-19 guidance

Week 1 Visit (+/- 3 days)

The following procedures can be carried out via phone or video call:

- ConMeds (check new or ongoing).
- AEs (check new or ongoing).

Patients will need to attend the hospital for a short visit to carry out the rest of the Week 1 procedures.

Month 6 (+/- 6 weeks)

The following procedures can be carried out via phone or video call:

- Questionnaires
- Dose titration (reducing dose/ stopping IMP only – based on AEs)
- ConMeds (check new or ongoing)
- AEs (check new or ongoing)
- IMP dispensing (see below)

Patients will need to attend the hospital to carry out the rest of the Month 6 procedures.

IMP supply to participants

Sites can arrange for the IMP study drug to be sent direct to the participants home. Verbal informed consent will be obtained and this will be recorded in the participant's records. An audit trail will be maintained from collection of the IMP by the courier to receipt by the participant.

6. Blinding

6.1. Definitions

In line with KCTU Standard Operating Procedures (SOPs) on blinding.

- ***Fully blinded*** **-** Not able to review any post Baseline outcome data coded as IMP/Placebo, or coded as A/B. All data should be presented aggregated across both allocation groups.
- ***Partially blinded*** **-** Able to review data post Baseline outcome data as A/B.
- ***Unblinded*** - Able to review post Baseline outcome data as IMP/Placebo.

6.2. Emergency un-blinding / code break

A 24hr telephone unblinding service will be provided for Emergency Code Break and Medical Information. This service will be provided by the ESMS Global Ltd. Each randomised patient will be provided with an information card detailing code break telephone numbers (020 3282 0458) and emergency contact details. A template for the alert card can be located in appendix 4. Participants will be requested to carry this card with them at all times whilst participating in the trial. After the patient has been unblinded, details will be requested from the PI using an unblinding form, further details will be provided in the study supporting material. Patients who are un-blinded will be withdrawn from the trial. Primary outcomes will be measured until the last patient last visit.

6.3. Blinding of trial personnel

At randomisation: Recruiting and consenting clinicians, researchers and senior statistician will all be blind to the allocation. Participants will be associated with a patient information number (PIN) and will not know their allocation (A or B). The KCTU randomisation system is linked directly to the IMP management system and pharmacy.

At Week 1: Participants will be assessed by blinded research nurses (RN) who ***will not be aware*** of the allocation. The RN will measure the participant heart rate and blood pressure, and any reason why the participant cannot be up-titrated if eligible e.g. side effects. This information will be entered onto paper source data worksheets, then an online system (electronic data

capture system [EDC]). Haemodynamic parameters and adverse event burden will be discussed with a trial clinician to ratify dose control.

At Week 6: Blinded assessors will contact the participants by telephone and will record any adverse events. All adverse events will lead to further assessment. AE information will be recorded on a paper source data worksheets and inputted into the trial database housed by KCTU, blinded from the senior statistician, clinicians and researchers.

At Months 6 to 36: Blinded outcome assessors will be used to report all standard of care procedure data, AEs and pill count as per Week 6 outcomes.

At the completion of the trial: A blinded assessor will review the participant notes for evidence of variceal bleed or mortality.

Throughout the trial, the Chief Investigator (CI) and Senior Statistician will be fully blind to treatment allocation and will only see pooled data for the duration of the trial. At the start of any TMG/TSC/DMC, the committee are to be reminded the CI and Senior statistician are fully blinded.

6.4. Planned un-blinding of trial personnel

Trial Manager - The trial manager is planned to be partially blinded in order to expedite safety data from the site Principal Investigator (PI) to the Chair of the DMC. If required at the discretion of the DMC, they will be fully unblinded. The Trial manager will not take part in any discussion that influences the early stopping of the trial at any Trial Management Group meetings.

Junior Statistician - The Junior Statistician will be fully blind until the first version of the Statistical Analysis Plan (SAP) is approved by the Trial Steering Committee (TSC). The SAP should be detailed enough so that it presents a clear and structured plan for the primary outcome, required data manipulation, and analysis. It should be written consistent with the KCTU Statistics SOP on generating a SAP (ST-03 Statistical Analysis Plan). All changes to the

SAP after approval by the TSC should authored by a statistician who is fully blind, this would be expected to be the Trial statistician (Dr Ben Carter). Any amendments the SAP will be approved by the TMG, and TSC.

After the first version of the SAP is approved by the TSC, the Junior statistician is planned to become partially-blinded and access patient level data coded as A/B. The Junior Statistician will then have access to the adherence data and be able to monitor and inform the DMC of the trial adherence of the participants. They will present the closed DMC report to the DMC members.

The Junior Statistician will not take part in any discussion that influences the early stopping of the trial at any TMG, TSC, or DMC meetings.

The final combined Trial Steering Committee and Data Monitoring Committee meeting

Prior to this meeting the Junior Statistician will generate the partially blinded data and analyses presented to the senior statistician (allocations as A and B). This will be interpreted by the Senior Statistician and they will check the analyses prior to the meeting (completing adequate quality control checks, outlined in the SAP).

At this meeting this analysis will be ***fully interpreted by the TMG/TSC/DMC.*** Following consensus, the Chair of the TSC will be provided with an envelope that will contain the allocation (intervention and control) to fully un-blind the CI, and trial team. Any amendments to the primary outcome analysis after this meeting will be explicitly stated with the main trial results.

KCTU Trials Pharmacist – The unblinded KCTU trials pharmacist will be responsible for monitoring IMP stock levels at sites. They will have knowledge of the number of patients at site on treatment allocation A or B. The trials pharmacist will provide quarterly reports to TMG on the bulk supplies held at sites and at the manufacturer, for the purposes of IMP reordering/manufacture.

7. Interim Analysis

No interim analysis is planned for efficacy or harm, beyond the feasibility pilot phase assessment.

Internal pilot studies

Two internal pilots are planned to determine the feasibility of the trial. Internal pilot one at 12 months after the first patient is recruited is carried out to demonstrate the ability of recruit sites and patients within the sites. The second internal pilot will be after 30 months to estimate the variceal bleed rate, so to determine if this trial is adequately powered to continue.

7.1. Internal pilot 1 (Recruitment and retention)

An internal pilot will be run at 12 months after recruitment opens, with the following Go/No Go progression:

1. To have opened at least 8 sites, with at least one patient randomised at each.
2. To have randomised at least 80 patients.
3. To have a retention rate of at least 70%.

If we ***meet the above criteria we will progress to month 30*** *to assess the* ***Internal pilot 2*** (estimation of the one-year bleed rate).

7.2. Internal pilot 2 (Estimation of variceal bleed rate in control arm)

The BOPPP trial team hypothesise that the IMP offers a potential benefit, but only if the annual variceal bleed rate is ***at least 4%***. Using ***control-arm*** patients only, assuming a one-year bleed rate of **4%**, with a sample size of 360 we will be able to estimate the variceal bleed rate in the control group with a 95% confidence interval of +/- 2%. Therefore, if the bleed rate less than this the following recommendations come into force:

- If the bleed rate is ***at least 4%*** the DMC should recommend to the TSC to continue the trial.

- If this is ***between 2 and 4%***, the DMC, will review the control arm bleed rate, and make a recommendation about increasing the trial length (or increasing the sample size). If this does occur, at this point we will approach the NIHR for additional funding to extend the trial.
- At month 30, if the one-year bleed rate in the control arm is ***less than 2%*** we can conclude that the bleed rate is lower than 4%. We will present the evidence to the DMC and request a recommendation to the TSC to stop the trial.

8. Assessment of Efficacy

8.1. Primary efficacy parameters

- Time till variceal haemorrhage (defined by Baveno IV criteria[14]) at the end of the trial
- Cost effectiveness of carvedilol in this population.

8.2. Secondary effectiveness and safety parameters

Secondary Endpoints (defined as at 3 years post baseline unless explicitly noted to be different)

- Estimation of the 1, and 3-year oesophageal variceal bleed rate by allocation, and associated number needed to treat
- Progression to oesophageal medium/large varices requiring clinical intervention over 3 years
- Composite of oesophageal variceal bleed or progression to medium/large varices over 3 years
- Progression of gastric, duodenal or ectopic varices
- Survival (Overall, liver-related, or cardiovascular-related)

Other outcomes

- Decompensation

  One of

  i. Spontaneous bacterial peritonitis (ascitic fluid cell count >250/mm3 polymorphs)

ii. Hepatic encephalopathy (defined by psychometric testing or clinical examination)

iii. New or worsening ascites defined by clinical examination or ultrasound

- Progression in Child Pugh grade (Appendix 5)
- Progression in MELD score (continuous) (Appendix 5)
- Quality of life, using the EQ-5D-5L

Other recorded events not defined as endpoints

a. Adverse Events (AE)
b. Serious AEs (SAE)
c. Adherence (pill counts)

8.3. *Procedures for assessing effectiveness parameters*

Oesophageal Variceal haemorrhage (defined by Baveno IV criteria)[14].

This is the primary reason for the potential use of NSBB in this cohort of patients. NSBB are hoped to prevent progression of portal hypertension to the point where VH occurs and thus prevent hospital admission and the risk of death associated with VH. The PPI group confirmed this as a patient supported preferred outcome.

Progression to medium/large oesophageal varices requiring clinical intervention:

This endpoint is an important pre VH outcome as at this point initiation of NSBB or pre-emptive endoscopic band ligation (EBL) is warranted. As continuing with a placebo may be dangerous in this cohort we define this as a trial endpoint.

Clinical intervention requiring initiation of NSBB (composite of oesophageal variceal bleed or progression to medium/large oesophageal varices):

This endpoint will capture both portal hypertension-related reasons for starting NSBB. Composite endpoints are encouraged by multiple expert groups in portal hypertension[15] and

this is a clinically relevant pragmatic composite that will define those patients who have or are at significant risk of bleeding due to progression of portal hypertension.

Survival/Mortality:

Will be assigned as liver related (following episode of variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome or acute on chronic liver failure) or cardio-vascular related (following episode of chest pain, arrhythmia, heart failure or proven cardiac ischaemia)). All-cause mortality will also be recorded.

All other clinical outcomes are not trial endpoints.

Child-Pugh score will be determined using serum albumin and bilirubin levels, prothrombin time and the degree of ascites (Appendix 6) and encephalopathy (Appendix 7).

The model for end stage liver disease (MELD) is an alternative prognostic scoring system based on standard laboratory investigations. MELD (Appendix 5) will be measured on all patients at randomisation and annually until the end of the trial. Progression in MELD or Child Pugh will be noted as an important clinical event.

9. Assessment of Safety

9.1. Planned un-blinding due to safety

In order to facilitate efficient management of safety reporting the trial manager will be un-blinded to allow allocation to be communicated to the DMC. The chief investigators and investigator team will all remain fully blinded throughout the duration of the trial. At the start of all TMGs there will be a standing agenda item that all co-applicants must remain fully blinded to the allocation and no reports, tables will be reported partitioned into the allocation groups (A or B).

The protocol contains criteria for un-blinding for safety reasons when clinicians need to know the allocation at the point when the patient leaves the trial and the TMG will be able to

facilitate based on these criteria without involving the co-applicants. In the rare circumstance a clinical safety query may require knowledge of the allocation the TMG will communicate directly with the chair of the DMC.

9.2. Procedures for reporting and recording adverse events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

- Adverse Event (AE): Any untoward medical occurrence in a participant to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.
- Adverse Reaction (AR): Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.
- Unexpected Adverse Reaction (UAR): 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 summary of product characteristics (SmPC).
- Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:
    - results in death;
    - is life-threatening;
    - required hospitalisation or prolongation of existing hospitalisation;
    - results in persistent or significant disability or incapacity;
    - consists of a congenital anomaly or birth defect;
    - requires intervention to prevent permanent impairment or damage; This includes important medical events (IMEs) that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above

should also be considered serious.

- Pregnancy: Although not a serious adverse event, any unplanned pregnancy will be reported via the SAE reporting system.

All adverse events should be graded by the most up to date Common Technology Criteria for Adverse Events (CTCAE) criteria (currently v5.0): A summary is below:

Grades: Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities for daily living (ADL)*. *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

9.3. Reporting responsibilities

King's College Hospital NHS Foundation Trust has delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the KHP King's Health Partners Clinical Trials Office

(KHP-CTO).

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24hrs) by the site PI or delegate to the KHP-CTO and CI for review in accordance with the current Pharmacovigilance Policy.

Death as a result of disease progression and other events that are primary or secondary outcome measures are not considered to be SAEs and should be reported in the normal way, on the appropriate CRF.

The KHP-CTO will report SUSARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial is taking place.

The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days;
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The Chief Investigator and KHP-CTO (on behalf of the *co*-sponsors), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually. The Trial Manager will report to the DMC.

9.4. Events that do not require reporting

- Medical events or the consequence of those events which occur prior to taking trial IMP, do not need to be reported.

- Planned elective admissions for emerging illnesses should not be considered SAEs.
- Medical events which are recognized complications of cirrhosis will not require reporting.
    - Variceal haemorrhage
    - Decompensation (trial endpoints) i.e. one of:
        1. Spontaneous bacterial peritonitis (ascitic fluid cell count >250/mm^3 polymorphs)
        2. Hepatic encephalopathy (defined by psychometric testing or clinical examination)
        3. New or worsening ascites defined by clinical examination or ultrasound and/or
    - Development of hepatocellular carcinoma
- Hospitalisation less than 24 hours (e.g. for therapeutic parascentesis / outpatient appointments)

All of the above will be required to be *recorded* in relevant sections of the source data worksheets and electronic data capture systems as part of ongoing data collection activities e.g. AE log.

9.5. Treatment stopping rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Data Monitoring & Trial Steering Committee, regulatory authority or ethics committee concerned. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

The trial can be recommended for stopping, based on a decision by the DMC, or by the Trial Sponsor, or Regulatory Authority/Ethics Committee, if there are sufficient safety concerns that may compromise the health or well-being of the trial participants.

10. Statistics

BOPPP is a UK based, Phase IV, multi-centre, randomised, controlled, blinded (participant, clinician, analyst), prospective trial of carvedilol versus placebo in patients with small oesophageal varices.

10.1. Sample size

10.1.1. Estimation of variceal bleed rate

There is debate and uncertainly of the variceal bleed rate within this population. More than 50% of patients with cirrhosis will develop varices during their lifetime. Many studies report on the rate of bleeding from small OV or progression to larger OV but with variable event rates. Garcia-Tsao et al[16] suggest a yearly rate of 5-15% from all varices with the lower rate attributed to small OV or patients with compensated cirrhosis. Merli et al[17] suggest a 2-year bleed rate of 12% and progression rate to larger OV of 31% at 3 years. De Francis suggests a higher rate of 20-30% at 2 years for all patients with varices[18]. Other authors suggest lower rates of VH from small varices of 8% at 2 years[19], or 4% per year in well compensated patients. In a small randomised control trial of Carvedilol in patients with small varices Carvedilol delayed progression to large varices over 2 years (21% in Carvedilol arm and 39% in placebo arm).

10.1.2. Sample size calculation

Given the uncertainty of the evidence for VH rates in patients with small OV we estimate a three-year event rate of 18% in the control arm (a bleed rate of 6% per year), we estimate a hazard ratio of 0.6 for those in the Carvedilol arm (with event rate in the Carvedilol arm of 11% over three years). To achieve 90% power with a type II error on 0.05, we will need to recruit 1072 patients. To account for 10% loss, we inflate this to 1200 patients.

10.2. Sample size calculation sensitivity scenarios

10.2.1. Lower variceal bleed rate

Given the uncertainty of the bleed rate, we performed a sensitivity analysis assuming lower bleed rates. If the three–year control arm event rate in the trial is 15%, the trial will retain 86% power, if this is 12.5% we will retain 78% power, this is approximately an annual rate of 4%. Given the importance of the bleed rate estimate we have a second internal pilot to test this assumption.

The BOPPP trial has a median follow up of 4 years, rather than 3 years, with the first patient having 5 years of follow up. This will inflate the number of variceal bleed events.

10.2.2. Higher hazard ratio

Should the hazard ratio rise to 0.7, but the event rate in the control arm remains the same the trial will retain 68% power.

10.3. Statistical analysis and quantitative data

10.3.1. Internal pilot 1

The feasibility outcomes will be calculated and summarised by the junior statistician. The junior statistician will have knowledge of allocation (A/B) to provide the report to the DMC. The DMC will assess the report against the Go / No go criteria and make a recommendation to the TSC.

10.3.2. Internal pilot 2

The junior statistician will summarise the 1-year variceal bleed rate, by arm and provide this to the DMC directly. The DMC will assess the report against the Go / No go criteria and make a recommendation to the TSC. Data and the blinded report will be stored in a KCTU area with restricted access.

10.3.3. Primary outcome

The time-till-variceal bleed for the two allocation groups will be analysed using a Cox's proportional hazards model, and adjusted for patient age, gender, and disease severity as

described in the SAP. Site will be fitted as a frailty effect. The assumption of proportionality will be visually assessed using a Kaplan Meier Plot, with an at-risk table for the two groups. We will report a hazard ratio, with associated 95% confidence interval and p-value.

10.3.4. Secondary outcome

Continuous data will be analysed using general linear mixed effects model, with random effects for patient, and adjusted for site, patient age, and disease severity as described in the SAP. The mean difference between allocation groups will be presented alongside 95% CI and p-value. Dichotomous outcomes will be analysed using a mixed effects logistic regression, similarly to the above. The various outcomes that will be recorded at the various scheduled trial visits are summarised in Table 2. These outcomes will be investigated using the intention to treat population.

Table 2: Outcome recording

Trial visit	Baseline	Week 1 (+/-3) days	Week 6 (+/-2) weeks	Month 6 (+/-6) weeks	Month 12 (+/-6) weeks	Month 18 (+/-6) weeks	Month 24 (+/-6) weeks	Month 30 (+/-6) weeks	Month 36 (+/-6) weeks	At variceal bleed	At trial completion (via registry)
Variceal bleed				X	X	X	X	X	X	X	X
Mortality			X	X	X	X	X	X	X	X	X
Hospitalisation			X	X	X		X		X		
Increase in grade of OV					X		X		X		
Presence of non-OV					X		X		X		
Progression in Child Pugh score				X	X	X	X	X	X	X	
Progression in MELD score				X	X	X	X	X	X	X	
Progression in UKELD score				X	X	X	X	X	X	X	
Progression in CLIF-C AD score				X	X	X	X	X	X	X	
Development of hepatic decompensation				X	X	X	X	X	X	X	
Heath Care usage	X			X	X	X	X	X	X	X	X
EQ-5D-5L Quality of Life Score	X			X	X	X	X	X	X	X	

10.3.5. Population under investigation

An intention to treat population (ITT) will include all patients in the outcome. Patients who experience a variceal bleed will be described as a treatment failure and event. Those who do not experience a variceal bleed within follow up will be recorded as a non-event and censored at the last time of follow up, including those that progress. Patients who do not have any recorded post baseline data will be excluded from the ITT population.

A per-protocol population (PPP) will exclude participants who are protocol violators. Participants who progress (e.g. due to increase in varices size), but have not experienced a variceal bleed will be censored in the analysis of primary endpoint.

10.3.6. Protocol deviations and violations

A protocol deviation/violation is defined if there is an unplanned excursion from the protocol as planned. A protocol deviation (PD) is defined as a non-serious breach from the protocol that is unlikely to lead to any impact on the value of the data contributing to the overall treatment effect. An example of a PD would be missing of a single visit window, or not returning the IMP bottle at a single visit. A protocol violation (PV) is an excursion from the protocol that is more serious and likely to lead to a significant impact on the quality of the data and would lead the patient from being excluded from the per protocol population. A detailed definition of the protocol deviation and violation will be presented in the Statistical Analysis Plan (SAP).

10.4. Health economic assessment

We will undertake cost-utility analyses of Carvedilol compared with usual care over a three-year time horizon and over a lifetime, from a Health and Personal Social Services perspective. Quality of life will be assessed at baseline and at 6 monthly intervals using the EQ-5D-5L. Resource use in secondary care will be assessed from Hospital Episode Statistics records (or equivalent for patients in Scotland, Wales or Northern Ireland). Primary care resource use will be collected using a patient questionnaire. Unit cost data from appropriate national sources

(NHS Reference Costs, Unit Costs of Health & Social Care etc.) will be applied to resource use. Cost effectiveness will be reported as the incremental cost-effectiveness ratio (ICER); mean incremental net monetary benefit (INMB) after valuing a quality adjusted life-year (QALY) at £20,000; and the cost-effectiveness acceptability curve (CEAC).

The 'within trial' analysis will compare costs and quality adjusted life expectancy (QALE) across trial arms with adjustment for pre-specified baseline characteristics. Missing data will be imputed by Multiple Imputation. Bootstrapping will be used to quantify the impact of sampling uncertainty and generate a CEAC. For the lifetime analysis, we will build a Markov model to extrapolate costs and estimate QALE. Health states will include compensated and decompensated cirrhosis, liver transplant, hepatocellular carcinoma, myocardial infarction, bleeding event and death. Costs and quality of life tariffs will be attached to health states and generated from the trial data, where possible, or from the literature. The model will be probabilistic; uncertainty in parameters will be quantified from the trial data or literature sources or estimated where necessary. Important event rates including bleeding events will be estimated from the trial data using parametric survival analysis. Alternative parametric specifications will be tested in sensitivity analysis. Results will be presented as the INMB, ICER (where appropriate) and CEAC. In the base case the analysis will assume no difference in quality of life according to treatment, conditional on the model health state, *provided* we observe no difference across trial arms at the 5% significance level. In sensitivity analysis we will adjust quality of life tariffs according to differences attributable to treatment (conditional on health state such as compensated cirrhosis) estimated from the trial data.

10.5. Qualitative data

Qualitative data will be transcribed verbatim and pseudo-anonymised to maintain confidentiality. Data will then be analysed iteratively using a focussed thematic analysis[20]. Three members of the research team will independently code initial data before constructing an analytical framework, which will be applied to the remaining transcripts, with themes and subthemes refined as necessary. Ideas about themes and their relationships will be recorded in theoretical memos and discussed among our Patient Advisory Group and Project Steering

Group. The computer programme QSR N-VIVO will be used to process the transcripts, enabling us to code and retrieve a large volume of narrative data. The trial will be conducted and reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement.

11. Trial Steering Committee

The Trial Steering Committee (TSC) will meet at the commencement of the trial, after MHRA and Ethics approval, either face-to-face or via teleconference (if face-to-face proves problematic), and thereafter every 6 months to one year to assess trial conduct and recruitment. The TSC members include the following <see Appendix 8>; independent chair, chief investigator, trial statistician, clinical co-applicants, patient representatives, qualitative researcher, independent clinicians. The TSC will approve the TSC charter and will be defined as quorate if at least 67% of the Independent members are present at the TSC.

12. Independent Data Monitoring Committee

The DMC will have 3 members <see appendix 8>; to review data on safety, including SAEs, SUSARs, and the primary endpoint events, and will advise the trial steering committee (TSC) on acceptable continuation of the trial, or whether the trial should be stopped. The DMC will meet via in person or by teleconference every 6 months to one year (and more frequently if deemed necessary). The composition and responsibilities of the DMC is outlined in the DMC Charter. The membership of the DMC will receive final approval from the NIHR as per the terms of the award. The DMC will approve the DMC Charter in line with Damocles. The DMC will be chaired by Prof Kenneth Simpson (University of Edinburgh) and will require 2 members present (in person, or by telephone) to be quorate.

13. Direct Access to Source Data Documents

The Investigators will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and

other documents (e.g. patients' case sheets, blood test reports, X-ray reports, histology reports etc.).

14. Ethics and Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP, and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for approval to the Health Research Authority (HRA) <Yorkshire & The Humber - Leeds West Research Ethics Committee> Research Ethics Committee (REC), and to the Medicines and Healthcare Products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

Subsequent protocol amendments will be submitted to the REC and Regulatory Authorities for approval (if applicable), and that you will comply with regulations, particularly specifying, Pharmacovigilance reporting and providing the REC & MHRA with progress reports, and a copy of the Final Trial Report.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations. The KHP CTO will upload the final report to EudraCT on behalf of the Sponsor.

15. Quality Assurance

Monitoring of this trial to ensure compliance with Good Clinical Practice and scientific integrity will be managed, and oversight retained, by the KHP-CTO Quality Team. Further details will be given in the data monitoring plan.

16. Data Handling and Management

Source data refers to the patient data held on clinical NHS systems. This will be entered onto a source data worksheet. The CI/PI is responsible for the accuracy of all data reported in the source data worksheet. The source data will therefore form part of the source data for this trial but original NHS systems data will be made available for monitoring purposes. The source data will be entered into a Infermed MACRO database from the source data worksheet. Each site will have a login to the database.

An electronic database provided by Infermed Macro will be used to capture trial related information. All data will be inputted using the source data worksheet and stored on a database to be analysed at the end of the trial.

Access to the Infermed MACRO database will be restricted, with only authorised site-specific personnel able to make entries or amendments to their patients' data. It is the investigator's responsibility to ensure completion and to review and approve all data captured in the MACRO database. The recruiting physician or his/her designee(s) will be responsible for all entries into the MACRO database and will confirm (electronically) that the data are accurate and complete.

16.1. Source data worksheet completion

The source data worksheet completion will be performed by members of the research team at each site; who have been delegated the task in the trial delegation of responsibilities log. Participant competed questionnaires will be stored with the source data worksheet.

16.2. Data handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to: Patient data will be pseudo-anonymised. All pseudo-anonymised data will be stored on a restricted access, password protected computer. All trial data will be processed, stored and disposed of in accordance with all relevant legal and regulatory

requirements, including the UK General Data Protection Regulation (GDPR) and any amendments thereto.

16.3. Data validation

Data will be validated at the point of entry into the eCRF and at regular intervals during the trial. Data discrepancies will be flagged to the trial sites and any data changes will be recorded in order to maintain a complete audit trail (e.g. reason for change, date change made, who made change). All trial data will be held securely at the KCTU. All transfers of data across the internet will be encrypted.

16.4. Record retention

To enable evaluations and/or audits from regulatory authorities, the investigators agree to keep records, including the identity of all participating patients (sufficient information to link records, all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition). The records should be retained by the trial site coordinators and investigator according to ICH GCP, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer.

16.5. End of trial definition

This is defined as when the database will be locked and will follow the KCTU statistical SOPs on generation of the final clinical trial report. The planned trial closure will form part of the TMG minutes. Final report submission will be within 12 months of end of trial.

16.6. Archiving

All written trial related documentation will be archived for 15 years after completion of the trial as per KHPCTO SOPs for CTIMPS. Electronic data will be stored in the TMF and archived. It is the responsibility of the site PI to make arrangements for appropriate archiving of trial related documentation.

17. Amendments

All amendments will be tracked in the BOPPP 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.

18. Publication Policy

It is intended that the whole or part of this results of the trial will be reported and disseminated at international conferences and in peer-reviewed scientific journals and by Open Access credentialing. The protocol will be published in a clinical trials journal during the first two years of the study commencing. No professional writers will be used. Full anonymity of participant's details will be maintained throughout. We will disseminate the results to our patients via the BOPPP website and to our partners in the British Liver Trust.

19. Insurance / Indemnity

KCH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. KCH will only extend NHS indemnity cover for negligent harm to its employees; substantive and honorary, conducting research studies that have been approved by the KCH Research and Innovation Office. KCH cannot accept liability for any activity that has not been properly registered and approved by the KCH Research and Innovation Office. Potential claims should be reported immediately to the KCH Research and Innovation Office:

Research and Innovation Office
King's College Hospital NHS Foundation Trust
161 Denmark Hill, London SE5 8EF
Phone: +44 (0) 20 3299 1980
Email kch-tr.research@nhs.net

20. Financial Aspects

Funding to conduct the trial is provided by the National Institute for Health Research Health Technology Assessment Board, UK (Reference 17/32/04).

Department of Health and Social Care Disclaimer

The views expresses are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

21. Signatures

20 NOV 2020

_____ _____

Chief Investigator Date

VISHAL PATEL

20 NOV 2020

_____ _____

Chief Scientific Investigator Date

MARK McPHAIL

20 NOV 2020

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Senior Trial Statistician Date

BEN CARTER

Appendix 1 – Varices size assessment & gastroscopy report photo-documentation

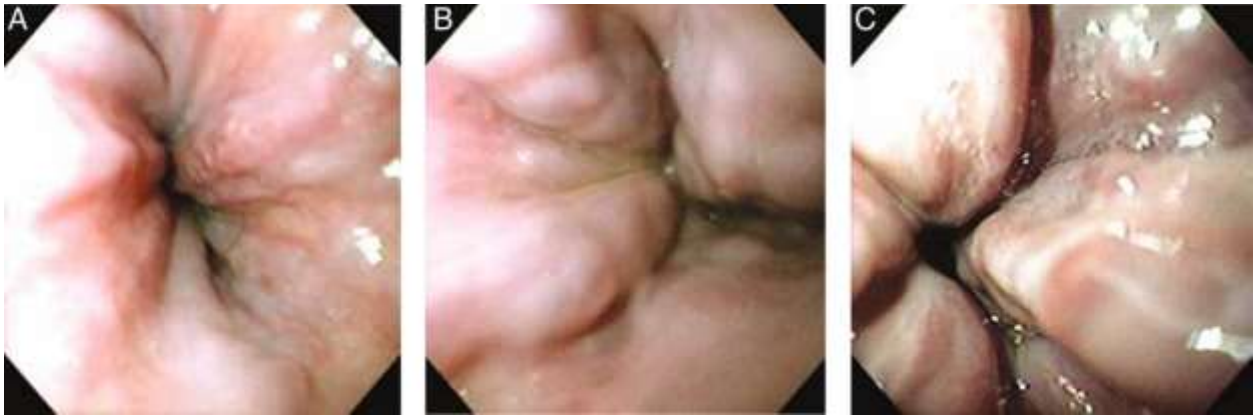

Figure Appendix 1A. Assessment of oesophageal varices. Reproduced with permission from Tripathi et al. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut* 2015; **64**(11): 1680-704

(A) Grade I oesophageal varices (or ≤5mm). These collapse to inflation of the oesophagus with air.

(B) Grade II oesophageal varices. These are varices between grades 1 and 3.

(C) Grade III oesophageal varices. These are large enough to occlude the lumen.

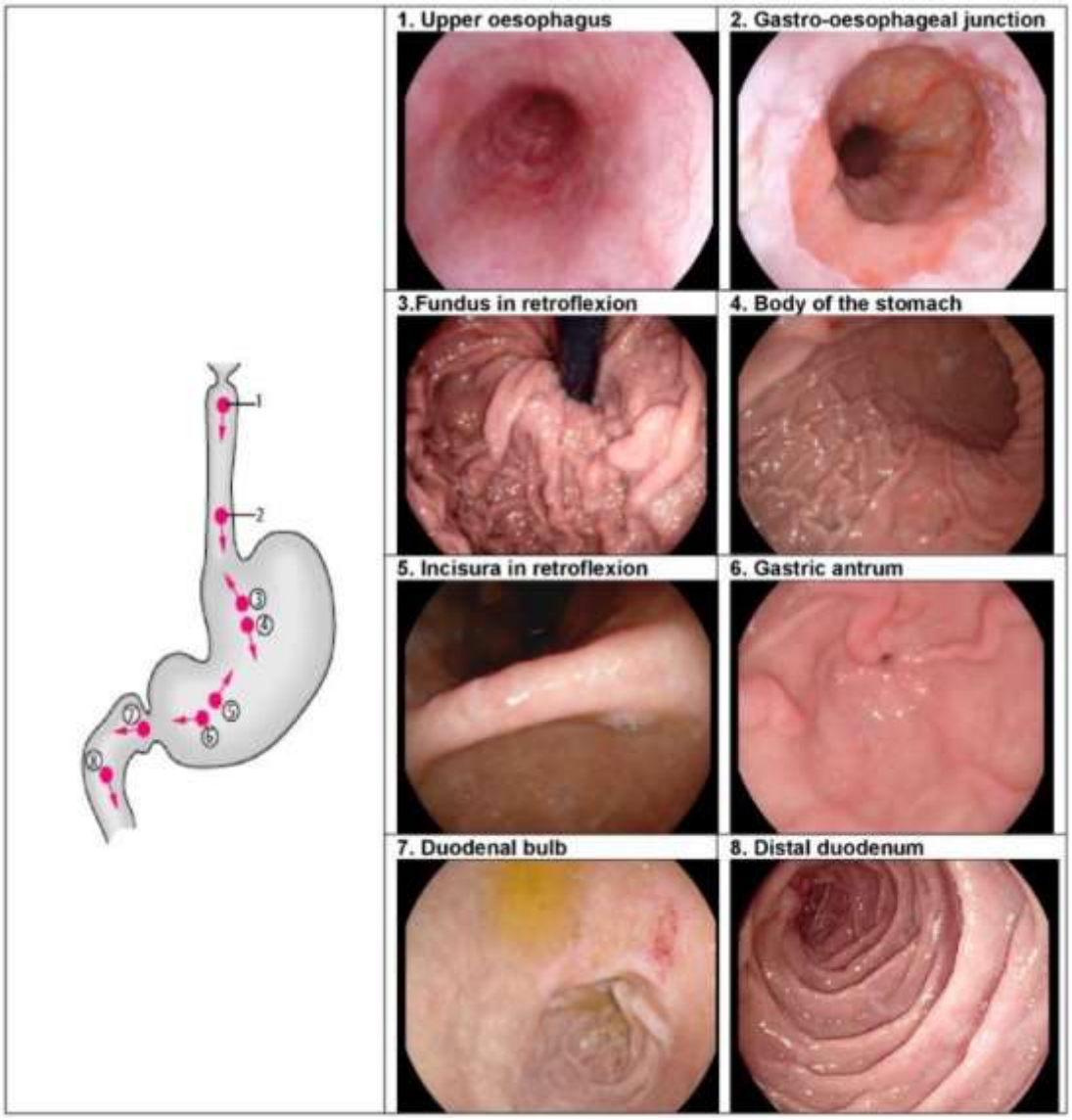

Figure Appendix 1B. A schematic demonstrating the recommended stations for photo-documentation during a diagnostic oesophago-gastro-duodenoscopy. Used with permissions from. Rey JF, Lambert R.. ESGE Quality Assurance Committee. ESGE recommendations for quality control in gastrointestinal endoscopy: guidelines for image documentation in upper and lower GI endoscopy. *Endoscopy 2001;33:901–3.* doi:10.1055/s-2001-42537

Appendix 2 – Dose titration procedures

The target haemodynamic response is a heart rate reduced by >25% from that at baseline or between 50-55 bpm. The target dose is 12.5 mg but if the above aim is met at 6.25 mg then the patient should remain on 6.25 mg. A "red flag" symptom is a grade 3 cardiac symptom requiring urgent investigation. For this trial we define this as cardiac chest pain or collapses since starting trial medication. Further details on cardiac and syncopal grading can be found here:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

As a safety measure, if HR is 56-60 bpm or SBP 91-100 mmHg a dose increase from 6.25 mg to 12.5 mg is not recommended.

Criteria to up-titrate:

- no red flags on history, AND
- HR >60 bpm, AND systolic BP >100 mmHg

Criteria to remain at present dose

- Already on 2 tablets (12.5 mg); AND
- HR 50-59 bpm; OR
- HR <75% of baseline

Criteria to stop IMP:

- >0 red flags on history, OR
- On 1 tablet AND
- HR <50 bpm OR systolic BP <90 mmHg

Criteria to dose reduce:

- on 2 tablets AND
- HR <50 bpm OR systolic BP <90 mmHg

Criteria to stop IMP temporarily (any criteria present, restart IMP when these issues have resolved)

- Critical illness with hypotension (systolic BP <90 mmHg)
- Spontaneous bacterial peritonitis
- Acute kidney injury
- Hyponatraemia (Na < 125 mmol/L)
- Sepsis / GI Bleeding
- To facilitate cardiac stress testing

Appendix 3 – Acute kidney injury criteria

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

	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

Appendix 4 – BOPPP participant alert card

The trial is sponsored and coordinated by a team at Kings College Hospital

Liver Research
Room 45, 2nd Floor On-Call Building
King's College Hospital
Denmark Hill
London, SE5 9RS
www.BOPPP-trial.org

V1.3: 02/10/2019 Protocol number: ISRCTN10324656

PRINCIPAL INVESTIGATOR:
Please fill in the details below
and on the right and give this card to the patient.

Name of patient			
Patient's PIN			
Date of randomisation			
Dose of trial drug			
Signature of researcher		Date	

EMERGENCY 24 HOUR UNBLINDING PROVIDER:
ESMS - 020 3282 0458

ALERT CARD

Please keep this card with you and show it to anyone giving you medical treatment.

If you require any medical treatment, the doctor named overleaf should be informed.

THIS PATIENT WAS RANDOMISED INTO THE BOPPP TRIAL (Carvedilol or Placebo).
Please inform the doctor named below if patient develops any medical problems within 36 months of randomisation.

Doctor's name	
Hospital	
Address	
Telephone	

Appendix 5 – Liver prognostic scoring systems

These should be calculated at baseline and 6 monthly visits and noted in the CRF. They are **not** required in the one-week up-titration assessment or 6-week telephone call. Calculation should ideally be performed using the website as described in the subheadings. The component parts will be recorded in the CRF.

A1.1 Child Pugh Score

Child Pugh Score should be calculated from the following website:

https://www.mdcalc.com/child-pugh-score-cirrhosis-mortality

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L	<34	34–50	>50
Serum albumin, g/L	>35	28–35	<28
INR	<1.7	1.7-2.3	>2.3
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

A1.2. MELD score

Calculate MELD score from the following website:

https://www.mdcalc.com/meld-score-model-end-stage-liver-disease-12-older

MELD now includes sodium as per the following document from OPTN.
https://optn.transplant.hrsa.gov/media/1575/policynotice_20151101.pdf

The following description uses the units mg/dl NOT umol/l.

Candidates receive an initial MELD(i) score equal to:

0.957 x Ln(creatinine mg/dL) + 0. 378 x Ln(bilirubin mg/dL) + 1.120 x Ln (INR) + 0.643

Laboratory values less than 1.0 will be set to 1.0 when calculating a candidate's MELD score.

The following candidates will receive a creatinine value of 4.0 mg/dL:

- Candidates with a creatinine value greater than 4.0 mg/dL
- Candidates who received two or more dialysis treatments within the prior 7 days Candidates who received 24 hours of continuous veno-venous hemodialysis (CVVHD) within the prior 7 days

The **maximum** MELD score is 40. The MELD score derived from this calculation will be rounded to the tenth decimal place and then multiplied by 10.

For candidates with an initial MELD score greater than 11, the MELD score is then re-calculated as follows:

MELD = MELD(i) + 1.32*(137-Na) – [0.033*MELD(i)*(137-Na)]

Sodium values less than 125 mmol/L will be set to 125, and values greater than 137 mmol/L will be set to 137.

A1.3. UKELD score

Calculate the UKELD score from the following link:

https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/2913/ukeld_calculator-2.xls

UKELD score = (5.395 x Ln (INR)) + (1.485 x Ln (Bilirubin)) + (3.13 x Ln (bilirubin))– (81.565 x Ln (Na)) +435

A1.4. CLIF-C-AD score

These can be calculated from the following website:

https://www.clifresearch.com/portals/0/calculadoras/CLIF-C_AD_Score.htm

Appendix 6 – Clinical grading of ascites

No ascites=none detected clinically or on imaging (ultrasound, CT or MRI)

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.

Appendix 7 – Grading of hepatic encephalopathy

West-Haven Criteria for HE 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

Patients without somnolence (Grade 0/1/2) should have the animal naming test performed. In one minute (timed by the clinician/researcher), the patient should attempt to name as many animals as possible. The number is noted. ANT < 10 = impaired; ANT > 15 unimpaired; ANT 11-14 borderline.

Appendix 8 – Trial Steering Committee and Data Monitoring Committee members

	Independent	Committee	Role
Prof Eleanor Barnes	Yes	Trial Steering Committee	Clinician and Chair
Dr Steven Masson	No	Trial Steering Committee	Clinician
Dr Sam Thomson	Yes	Trial Steering Committee	Clinician
Dr Charles Millson	Yes	Trial Steering Committee	Clinician
Dr Helen Ashdown	Yes	Trial Steering Committee	Clinician
Dr Alan Watkins	Yes	Trial Steering Committee	Statistician
Dr Claire Snowdon	Yes	Trial Steering Committee	Qualitative Social Sciences
Dr Vishal Patel	No	Trial Steering Committee	Chief Investigator
Dr Ben Carter	No	Trial Steering Committee	Statistician
Ms Elaine Mullings	Yes	Trial Steering Committee	PPI
Ms Morwenna Orton	Yes	Trial Steering Committee	PPI
Mr Peter Walsh	Yes	Trial Steering Committee	PPI
Dr Ken Simpson	Yes	Data Monitoring Committee	Clinician and Chair
Dr Jeremy Cobbold	Yes	Data Monitoring Committee	Clinician
Dr Stephanie MacNeill	Yes	Data Monitoring Committee	Statistician

Appendix 9 – MBOP sub-study summary

Background

MBOP has been established as an isolated basic science mechanistic sub-study to investigate the mechanism of effect of carvedilol in preventing decompensation in patients with cirrhosis. The underlying mechanism of the benefit of beta-blockade will be characterised by measuring bacterial DNA, markers of gut permeability, phenotyping the subsequent immune response and gut microbiome in a subset of 600 patients enrolled onto BOPPP. Selected BOPPP sites with -80oC freezer facilities will be offered the opportunity to participate in MBOP, please email the BOPPP Trial management team to confirm site eligibility for the sub-study at kch-tr.boppptrial@nhs.net. As MBOP is a sub-study, this study is neither funded nor regulated by the NIHR.

Aims and objectives

1. Determine whether it is feasible to undertake the MBOP study.
2. Determine the clinical effectiveness of the reduction in all cause decompensation in patients treated with carvedilol versus placebo after 3 years.
3. Determine if circulating bacterial DNA levels are reduced by treatment with carvedilol.
4. Confirm that the gut microbiome itself is not modulated by carvedilol but that gut permeability itself is reduced.
5. Demonstrate that pro-inflammatory responses and monocyte phenotype and function are mediated with carvedilol via reduction in circulating bacterial DNA.

Eligibility

In order to be eligible for MBOP participants must meet the following eligibility criteria:

Inclusion Criteria - Consented onto the BOPPP Trial and randomised to receive IMP

Exclusion criteria - Subjects with pre-existing conditions which alter gut permeability as recorded by a clinician (inflammatory bowel disease, gastric surgery)

Consent

Eligible BOPPP subjects will be provided with the MBOP patient information sheet and have the sub study explained verbally. After participants have had the opportunity to ask questions and those agreeing to take part will sign the MBOP consent form. It is thought that there will be a minimal impact on the recruitment and retention of patients recruited to the main study due to the sub-study. The burden of the sub-study on the patients is low, and they are free to decline participation in the sub-study without affecting their participation in the main study.

Sample Collection

The below blood samples (N=600) will be collected at baseline and annually at years 1, 2 and 3

- 4ml EDTA tube whole blood for bacterial and host DNA quantification and profiling
- 6ml plain serum tube for cytokine profiling and future metabolic profiling
- 6ml PACSgene tube whole blood for RNAseq
- 2x8ml Cell preparation tubes for PBMC isolation and plasma aliquot storage

All blood samples will be shipped to KCL for central processing. In a subset of these participants (N=200), saliva and faecal samples will be taken at baseline and annually at years 1, 2 and 3. Saliva and faecal samples will be stored at KCL until they are analysed by a Human Tissue Authority licenced vendor.

- 8ml of saliva by passive drool
- Single 20ml universal container to obtain 15-20g of faeces

Future analysis will be conducted in Quadram Institute Bioscience, Norwich.

All MBOP samples will be stored, shipped and processed according to the MBOP lab manual.

Additional imaging (at KCH only)

Participants will have an additional scan of their spleen at baseline and annually at years 1, 2 and 3.

Appendix 10 – References

1. Williams R, Aspinall R, Bellis M, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. *Lancet* 2014; **384**(9958): 1953-97.

2. Mehta G, Gustot T, Mookerjee RP, et al. Inflammation and portal hypertension - the undiscovered country. *J Hepatol* 2014; **61**(1): 155-63.

3. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; **63**(3): 743-52.

4. Tripathi D, Stanley AJ, Hayes PC, et al. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut* 2015; **64**(11): 1680-704.

5. Augustin S, Altamirano J, Gonzalez A, et al. Effectiveness of combined pharmacologic and ligation therapy in high-risk patients with acute esophageal variceal bleeding. *Am J Gastroenterol* 2011; **106**(10): 1787-95.

6. Leithead JA, Rajoriya N, Tehami N, et al. Non-selective beta-blockers are associated with improved survival in patients with ascites listed for liver transplantation. *Gut* 2015; **64**(7): 1111-9.

7. Tripathi D, Ferguson JW, Kochar N, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. *Hepatology* 2009; **50**(3): 825-33.

8. Garcia-Tsao G. The Use of Nonselective Beta Blockers for Treatment of Portal Hypertension. *Gastroenterology & hepatology* 2017; **13**(10): 617-9.

9. Garcia-Tsao G, Lim JK, Members of Veterans Affairs Hepatitis CRCP. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program. *Am J Gastroenterol* 2009; **104**(7): 1802-29.

10. Longacre AV, Imaeda A, Garcia-Tsao G, Fraenkel L. A pilot project examining the predicted preferences of patients and physicians in the primary prophylaxis of variceal hemorrhage. *Hepatology* 2008; **47**(1): 169-76.

11. Serste T, Melot C, Francoz C, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. *Hepatology* 2010; **52**(3): 1017-22.

12. Reiberger T, Ulbrich G, Ferlitsch A, et al. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. *Gut* 2013; **62**(11): 1634-41.

13. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health economics* 2018; **27**(1): 7-22.

14. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2005; **43**(1): 167-76.

15. Abraldes JG, Garcia-Tsao G. The Design of Clinical Trials in Portal Hypertension. *Semin Liver Dis* 2017; **37**(1): 73-84.

16. Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding--unresolved issues. Summary of an American Association for the study of liver diseases and European Association for the study of the liver single-topic conference. *Hepatology* 2008; **47**(5): 1764-72.

17. Merli M, Nicolini G, Angeloni S, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. *J Hepatol* 2003; **38**(3): 266-72.

18. de Franchis R, Primignani M. Natural history of portal hypertension in patients with cirrhosis. *Clin Liver Dis* 2001; **5**(3): 645-63.

19. Zoli M, Merkel C, Magalotti D, et al. Natural history of cirrhotic patients with small esophageal varices: a prospective study. *Am J Gastroenterol* 2000; **95**(2): 503-8.

20. Braun V, Clarke V. What can "thematic analysis" offer health and wellbeing researchers? *International journal of qualitative studies on health and well-being* 2014; **9**: 26152.