BOPPP Trial Synopsis

Trial name: **B**eta blockers **O**r **P**lacebo for **P**rimary **P**rophylaxis of oesophageal varices in cirrhosis (BOPPP). A triple blinded, multi-centre, clinical- and cost-effectiveness randomised controlled trial.

Summary: BOPPP is an NIHR HTA funded multi-centre trial to examine the efficacy using the non-selective beta-blocker Carvedilol as primary prophylaxis to prevent variceal haemorrhage in patients with cirrhosis and small oesophageal varices. It will be one of the largest ever portal hypertension trials in this group of patients, with 83 patient participants recruited to date (Feb 2020) of a total of 1,200. BOPPP is currently being run at 24 UK-wide sites, with a further 25 sites being invited to open to recruitment over the next 6 months. Please contact **kch-tr.boppptrial@nhs.net** for further information.

Study design: Multi-centre, blinded, randomised controlled trial (RCT) of non-selective beta blockade (NSBB) *vs* placebo in patients with small oesophageal varices (OVs).

Funder: National Institute of Health Research Health Technology Assessment programme: £2.3 million.

Setting: Secondary and tertiary care centres with endoscopy and gastro-hepatology services – 50+ NHS hospital sites planned across the UK. **We have opened 24 sites and are looking for further sites to work with.**

Target population: Patients with cirrhosis and small OVs. Number of patients to be recruited: 1,200.

Inclusion Criteria:

- Cirrhosis (defined by two of clinical, biochemical, radiological and/or histological criteria)
- Grade 1 OVs without red signs at screening or surveillance endoscopy
- No episode of previous overt upper GI bleeding attributed to OVs
- Capacity to consent

Exclusion Criteria: Age <18, unable to give informed consent, unable to undergo screening gastroscopy, pregnancy/lactating, history of overt upper GI bleeding attributed to OVs, previous portosystemic shunt, gastroduodenal ulceration, already on a beta-blocker, requirement for beta-blockade (known portal hypertension/decompensation/cardiovascular disease), known allergy/intolerance/contraindication to beta-blockers, baseline heart rate (HR) <50bpm, baseline systolic blood pressure <85mmHg, active malignancy.

Intervention: Placebo or carvedilol 6.25mg once daily dose adjusted to 12.5mg after a week if tolerated or if HR <50-55 bpm is reached. 1:1 randomisation ratio.

Primary outcome: Variceal haemorrhage within 3 years, cost-effectiveness.

Secondary outcomes: All-cause mortality, increase in OV grade, hospitalisation with decompensated cirrhosis, MELD score increase, development of overt hepatic encephalopathy (HE), ascites, jaundice, renal impairment, HCC, myocardial infarction, liver transplantation.

Study visits: Screening, randomisation, week 1 following initiation of IMP for dose escalation, telephone call at 6 weeks. Every 6 months thereafter over 3-year follow-up period, aligned with standard of care clinical visits for hepatological assessment and HCC surveillance. Annual varices surveillance gastroscopies as standard of care.

Measurements of costs and outcomes: Variceal bleeding will be recorded at presentation, or hospital record, at year 3. Secondary outcomes will be recorded from hospital records, case report form (CRF), or mortality registry. Health care costs will be assessed using hospital records and CRF. Quality Adjusted Life Expectancy will be estimated from quality of life measurement at 6 monthly intervals using the EQ-5D-5L. Cost-utility will be determined at 3 years, and at lifetime using a Markov model.

Difference between current and planned care pathways: IMP checks, health related quality of life questionnaire.

Project timetable and recruitment: 24 months of recruitment of patients aiming for a total of 1,200 patients, with at least 3 years follow up of each patient.

Endorsements: 1) BASL-BSG Liver Research Development Group
2) British Liver Trust
BASL: British Association for Study of the Liver
BSG: British Society of Gastroenterology

Trial sponsor: Kings College Hospital NHS Foundation Trust

Chief Investigator: Dr. Vishal C. Patel
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BOPPP Trial Summary (in plain English)

Cirrhosis or liver scarring is an important problem in healthcare in the United Kingdom. 60,000 patients are living with this disease and about 11,000 people every year will die because of it. There are several ways in which patients with this severe form of liver disease become unwell or die and bleeding from the oesophagus or stomach is one. Cirrhosis causes pressure changes inside the abdomen and swelling of veins in the oesophagus (called "varices") which can bleed catastrophically.

We know that when varices are large, we need to treat them with medication called beta-blockers to reduce the pressure in the varices. If the varices are small, we are not sure if we need to treat with beta-blockers and this study aims to address this uncertainty. Patients who are recruited to the study with small varices will be randomised to either beta-blockers or a placebo. We will observe them closely for 3 years for bleeding from their varices or other complications of cirrhosis or side effects of taking medication. This is the amount of time needed to observe for bleeding when the varices are small. We will review the patients every 6 months including assessing the varices by a camera test called an endoscopy at the beginning and each year until the study is finished.

During the study patients will be involved with the conduct and management of the research, and we will feedback to recruited patients the results at the end. We will assess the barriers and facilitators of doctors in primary care - such as General Practitioners - in adjusting the dose of the tablets to optimise treatment effects, and assess patients' views on taking part in the trial, and whether the side effects justify the potential benefits of reducing the risk of bleeding. We estimate this risk could be reduced from 20% of patients having significant bleeding to 10% over 3 years.

We will measure the impact of beta-blockers on the overall costs to the NHS of caring for people with cirrhosis during the trial. We will then assess the impact of treatment on both mortality and quality of life using a combined measure, the Quality Adjusted Life-Year (QALY). We will use a mathematical prediction model to estimate the impact of treatment on costs, mortality and quality of life over a patient's lifetime. We will assess whether any increased costs are justified by better outcomes for patients and represent good value for money for the NHS budget.

Finally, we will publish the results of the study in the medical literature and discuss the findings at medical conferences, patient groups and with charities involved in helping patients with cirrhosis such as the British Liver Trust.

BOPPP Trial Flow Chart