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.

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 – 25 NHS hospital sites planned across the UK.

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.

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 investigative product for dose escalation, telephone call at 6 weeks and then every 6 months over a 3 year follow-up period. Annual varices surveillance gastroscopies as standard of care.

Health technology being assessed: Investigational Medicinal Product (IMP) - Carvedilol.

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, health related quality of life questionnaire.

Project timetable and recruitment rate: Initial scoping study at King's College Hospital of (160 patients) then further 18 months of recruitment of patients (aim-1,200 patients over the 2-year period), with at least 3 years follow up.

Expertise in team: KCH hosts the largest comprehensive clinical hepatology service in Europe and draws on national referral pathways to enhance study recruitment. King's Clinical Trial Unit (KCTU) has extensive methodological, trial design, statistics, health economics and qualitative research, with a proven track record of delivering large multi-centre RCTs. A UK wide collaborative group have pledged support to this study.

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

Co-Chief Investigators: Dr. Vishal C. Patel
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Trial Steering Committee members: *To Be Confirmed*

Data Monitoring and Ethics Committee members: *To Be Confirmed*

Trial Management Group members: *To Be Confirmed*