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
(Honorary Consultant Hepatologist (KCH), Honorary Senior Lecturer (KCL) & Principle Investigator (Institute of Hepatology, Foundation for Liver Research)

Dr. Mark . J. W. McPhail
(Senior Lecturer(KCL) & Honorary Consultant in Liver Critical Care & Hepatology(KCH))

Trial Steering Committee members: *To Be Confirmed*

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

Trial Management Group members: *To Be Confirmed*

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.

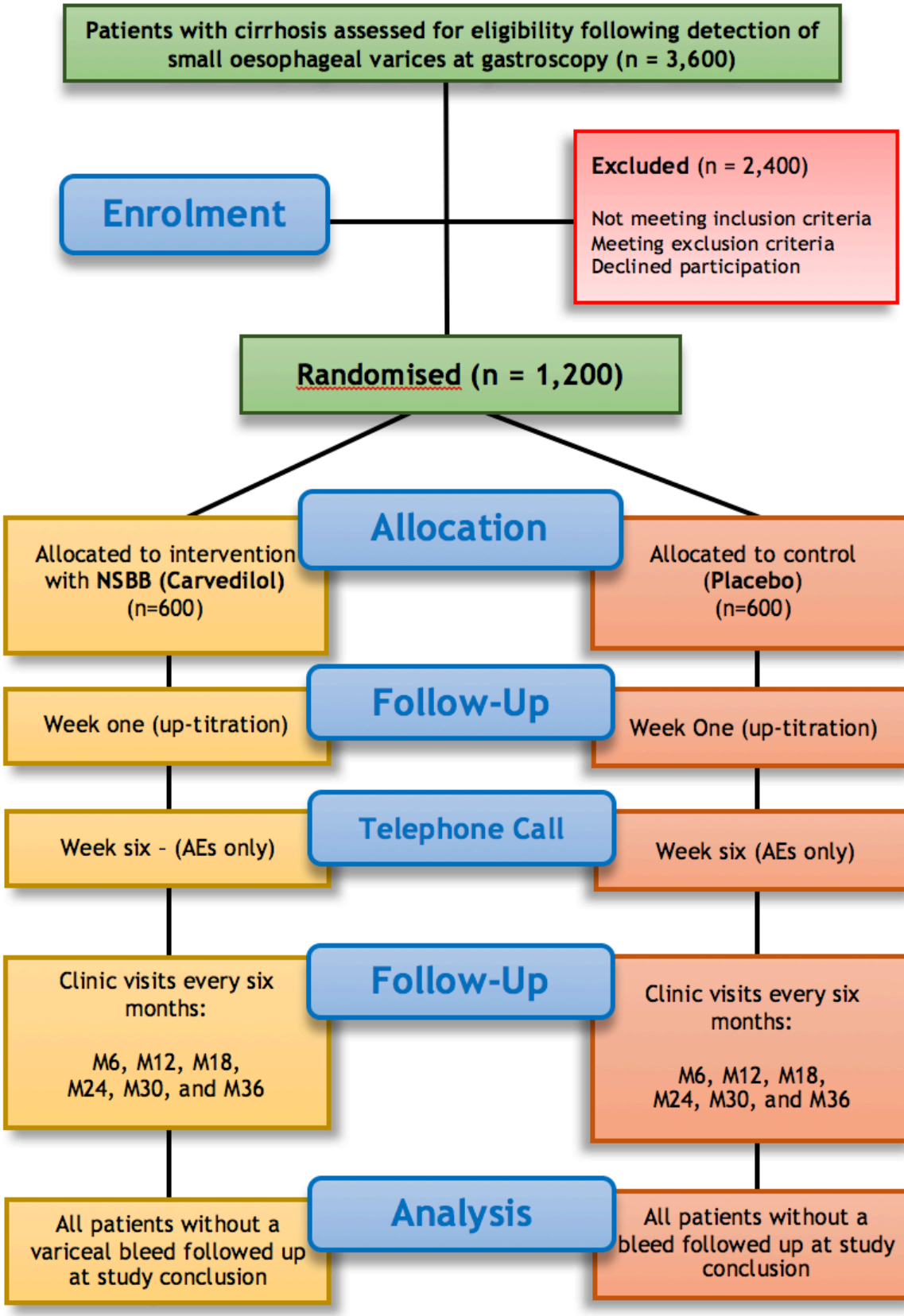
We know that when varices are large we need to treat them with medication called beta-blockers to reduce the pressure in the varices. If the varices are small, we are not sure if we need to treat with beta-blockers and this study aims to address this uncertainty. Patients who are recruited to the study 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



About King's College Hospital

The Liver Unit at King's College Hospital has a world class reputation for the treatment of liver related disorders with an extremely comprehensive set of services for the management of patients with liver failure, cirrhosis, liver cancer and portal hypertension. It also has one of the highest throughput of acute hepatology and liver transplants in Europe. Linked to this impressive clinical service is and one of the most active research environments in clinical trials, translational and basic science studies related to liver disease.

About King's College London

King's College London is one of the top 25 universities in the world (2016/17 QS World University Rankings) and among the oldest in England. King's has more than 26,500 students (of whom nearly 10,400 are graduate students) from some 150 countries worldwide, and nearly 6,900 staff. The university is in the second phase of a £1 billion redevelopment programme which is transforming its estate.

King's has an outstanding reputation for world-class teaching and cutting-edge research. In the 2014 Research Excellence Framework (REF) King's was ranked 6th nationally in the 'power' ranking, which takes into account both the quality and quantity of research activity, and 7th for quality according to Times Higher Education rankings. Eighty-four per cent of research at King's was deemed 'world-leading' or 'internationally excellent' (3* and 4*). The university is in the top seven UK universities for research earnings and has an overall annual income of more than £600 million.

King's has a particularly distinguished reputation in the humanities, law, the sciences (including a wide range of health areas such as psychiatry, medicine, nursing and dentistry) and social sciences including international affairs. It has played a major role in many of the advances that have shaped modern life, such as the discovery of the structure of DNA and research that led to the development of radio, television, mobile phones and radar.

About King's Health Partners

King's College London and Guy's and St Thomas', King's College Hospital and South London and Maudsley NHS Foundation Trusts are part of King's Health Partners. King's Health Partners Academic Health Sciences Centre (AHSC) is a pioneering global collaboration between one of the world's leading research-led universities and three of London's most successful NHS Foundation Trusts, including leading teaching hospitals and comprehensive mental health services. For more information, visit: **www.kingshealthpartners.org.**

About the National Institute for Health Research

The National Institute for Health Research (NIHR): improving the health and wealth of the nation through research. Established by the Department of Health and Social Care, the NIHR:

- funds high quality research to improve health
- trains and supports health researchers
- provides world-class research facilities
- works with the life sciences industry and charities to benefit all
- involves patients and the public at every step

For further information, visit the NIHR website ***www.nihr.ac.uk***

About the use of patient data

This work uses data provided by patients and collected by the NHS as part of their care and support and would not have been possible without access to this data. The NIHR recognises and values the role of patient data, securely accessed and stored, both in underpinning and leading to improvements in research and care. ***Read more:***
(https://www.nihr.ac.uk/about-us/our-purpose/principles/patient-data.htm)