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 die because of it. Cirrhosis causes pressure changes inside the abdomen and swelling of veins in the oesophagus (the tube that leads from the mouth to the stomach), these are called “varices” and 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 these veins. If the varices are small, we don’t know if this works. That’s why we’re doing this research.

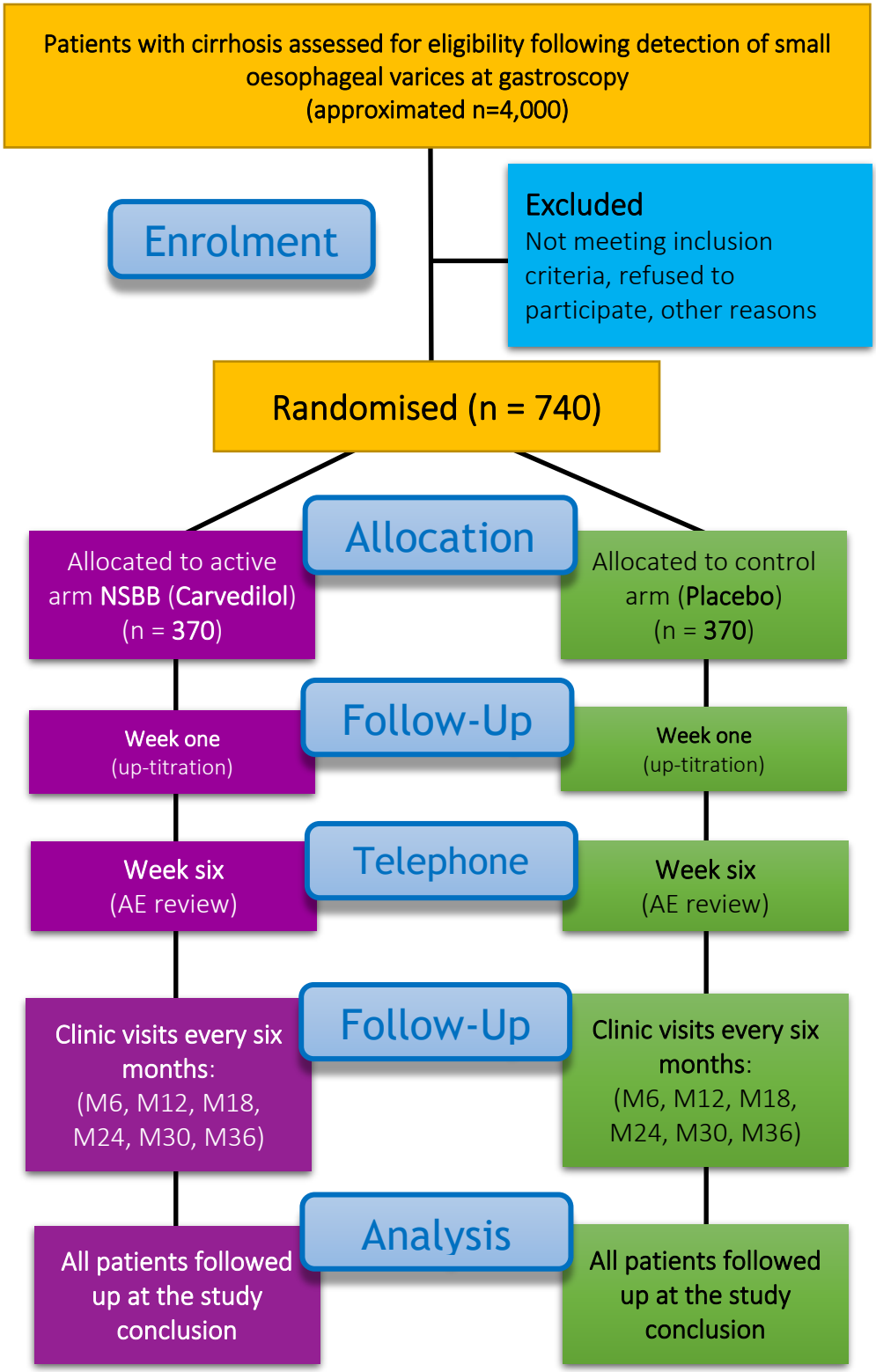
Patients with small varices who are recruited to the study will be randomly selected to receive either beta-blockers or a placebo. We will keep a careful eye on them to check for bleeding, complications, or side effects from the medicine. This will continue for three years to make sure so that we can be sure the results are right. Participants will be reviewed every six months over this period and it will involve some additional tests.

Cirrhosis patients collaborated in the design of the study and continue to be involved with the conduct and management of the research. We will find out how participants feel about taking part in the trial, and whether they think the side effects justify the potential benefits of reducing the risk of liver disease complications. We think that the risk of liver disease getting worse could go down by about 40% in three years, by using NSBB. We will also 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. This will help to make sure that better care is provided to patients in future.

We will assess the impact of treatment on both mortality and quality of life. We will also measure the impact of beta-blockers on the overall costs to the NHS of caring for people with cirrhosis during the trial. Then 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 the outcomes for patients are 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. We will ensure that participants know the results of the research as well as patient groups and charities involved in helping patients with cirrhosis such as the British Liver Trust.

BOPPP Trial Flow Chart



BOPPP Trial Synopsis

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

Study design: Multi-centre, blinded, 1:1 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: £2.5 million.

Setting: Secondary and tertiary care centres with endoscopy and gastro-hepatology services – 55 NHS hospital sites planned across the UK.

Target population: Patients with cirrhosis and small Oesophageal Varices (OVs). Number of patients to be recruited: 740.

Inclusion Criteria: Cirrhosis (defined by two of clinical, biochemical, radiological and/or histological criteria), grade 1 OVs without red signs diagnosed via surveillance endoscopy within last 6 months of screening.

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, current or previous medium/large oesophageal varices, gastric, duodenal, rectal or other ectopic varices, previous variceal haemorrhage, previous band ligation or glue injection of oesophageal and/or gastric varices, Child Pugh C cirrhosis, graft cirrhosis post liver transplantation, evidence of active malignancy without curative therapy planned, already on a beta-blocker, requirement for beta-blockade (decompensation/cardiovascular disease), known allergy/ intolerance/ contraindication to beta-blockers, baseline heart rate (HR) <50bpm, baseline systolic blood pressure <85mmHg, clinical symptoms consistent with COVID-19 at baseline.

Intervention: Placebo or carvedilol 6.25mg once daily dose adjusted to 12.5mg after a week if tolerated and HR >60 bpm and SBP>100mmHg.

Primary outcome: Time to first decompensating event; determining the clinical and cost-effectiveness in reduction of all-cause decompensation in patients treated with carvedilol or placebo.
All-cause decompensation defined by:

- Variceal bleeding
- New or worsening fluid buildup in the abdominal cavity
- New or worsening hepatic encephalopathy (brain dysfunction/ confusion)
- Spontaneous bacterial peritonitis (infection in fluid)
- Hepatorenal syndrome (kidney failure)
- Child Pugh score progression by 1 grade or MELD score by 5 points,
- Liver-related mortality

Secondary outcomes: All-cause mortality, increase in OV grade, development of gastric, duodenal or ectopic varices, quality-of-life, EQ-5D-5L.

Study visits: Screening, baseline and 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. Other complications within definition of all-cause decompensation and 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.

Project timetable and recruitment rate: Approximately a 5-year recruitment period with the aim of recruiting 740 patients with up to 3 years follow-up.

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

A UK wide collaborative group have pledged support to this study.

Trial sponsor:
Kings College Hospital NHS Foundation Trust

Chief Investigator:
Dr Vishal Patel
Honorary Consultant Hepatologist (KCH)
Honorary Senior Lecturer (KCL)
Principle Investigator (Institute of Hepatology, Foundation for Liver Research)

Chief Scientific Investigator:
Dr Mark McPhail
Senior Lecturer (KCL)
Honorary Consultant in Liver Critical Care & Hepatology (KCH)

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 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)