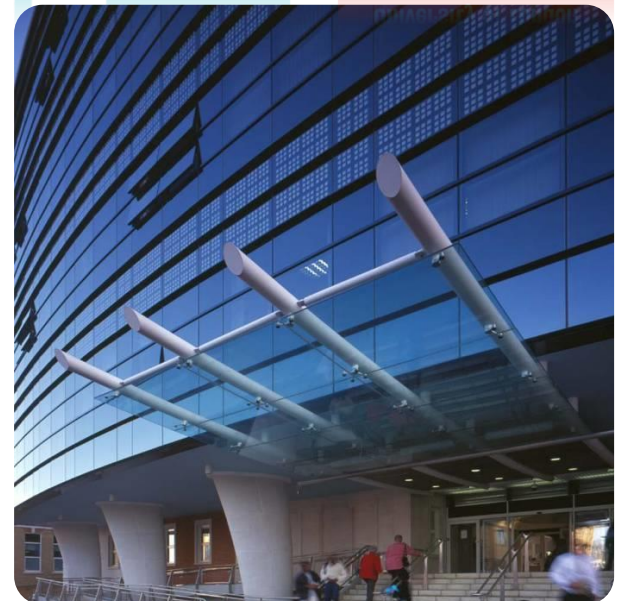




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Beta blockers Or Placebo for Primary Prophylaxis of oesophageal varices



- NIHR Health Technology Assessment commissioned grant call
- Application supported closely by KCL Clinical Trials Unit
- **£2.3 million** award – King's College Hospital
- CHIEF INVESTIGATOR: **Vishal Patel**
- CHIEF SCIENTIFIC INVESTIGATOR: **Mark McPhail**
- TRIAL MANAGER: **Kieran Brack**

- **Trial Design:** Multi-centre, phase IV, triple blinded (participant, investigator, analyst), prospective RCT
- **Purpose:** To determine if carvedilol reduces rate of variceal haemorrhage (VH) in patients with cirrhosis and small oesophageal varices (OV)
- **Primary objective(s):** To determine the clinical and cost effectiveness of the reduction in VH in patients treated with carvedilol vs placebo after 3 years.
- **Secondary objectives:** all-cause mortality, increase in OV size, hospitalisation with decompensation, MELD score increase, development of overt hepatic encephalopathy (HE), ascites, jaundice, renal impairment, HCC, myocardial infarction, liver transplantation. NSBB optimisation in 1o care
- **Target population & setting:** 1,200 cirrhotic patients with small OV to be recruited across 20 UK NHS sites, each f/u for 3 years

Primary Endpoints

1. Time to first variceal haemorrhage
2. Cost-utility of NSBB over trial follow up to 3 years.

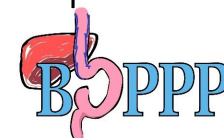
Secondary Endpoints

From baseline to 3 years:

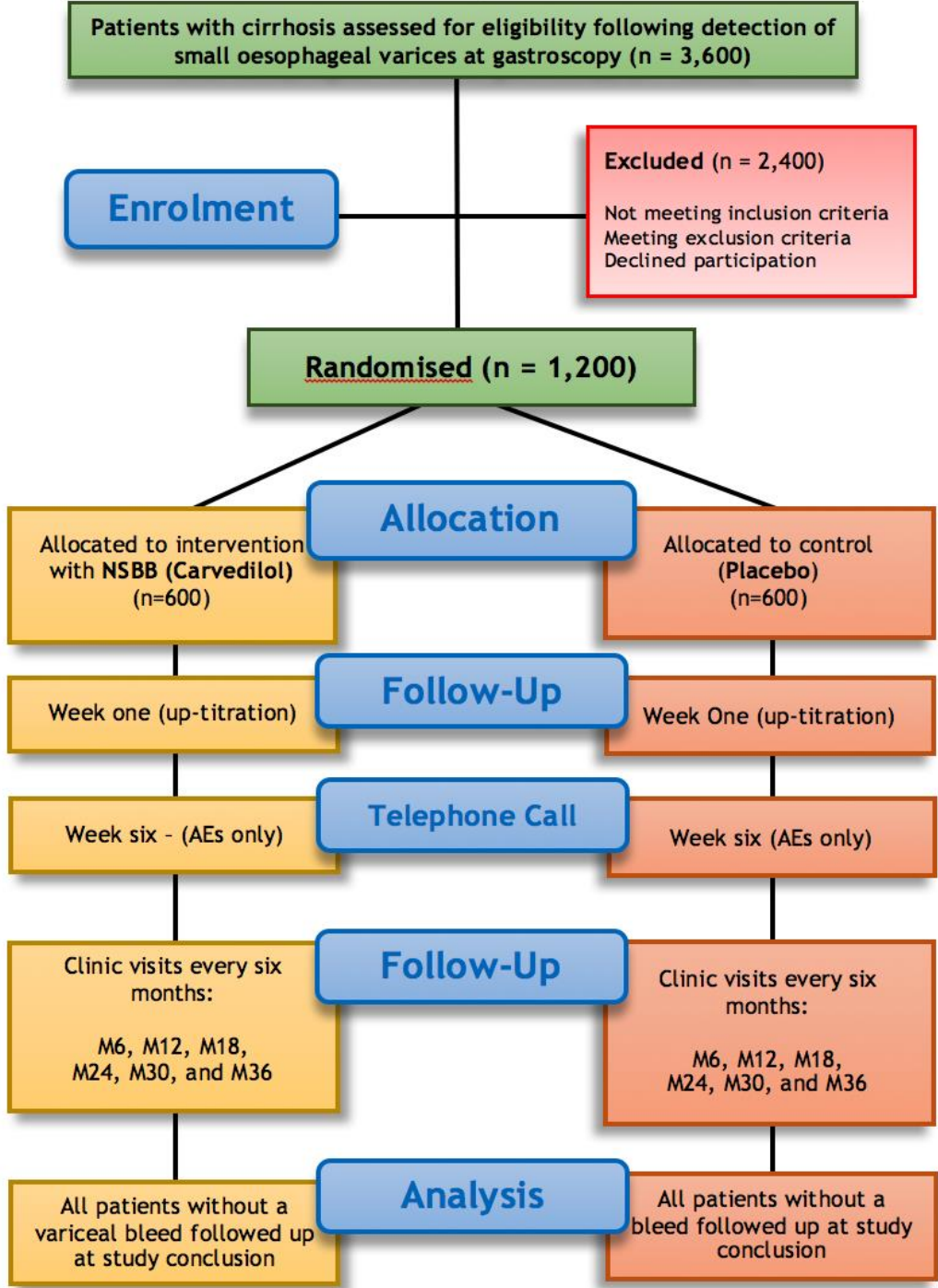
1. Estimation of the 1 and 3-year variceal bleed rate by allocation, and associated number needed to treat
2. Progression to medium/large varices requiring clinical intervention
3. Composite of progression in variceal size or bleeding as per (1) and (2) by 3 years
4. Clinical decompensation (new ascites, SBP, new hepatic encephalopathy)
5. Progression in Child Pugh grade
6. Progression in MELD score (continuous)
7. Survival (Overall, liver related, cardiovascular related)
8. Quality of life, EQ-5D-5L
9. Healthcare usage

- ✓ Cirrhosis and portal hypertension defined by any 2 of:
 - ✓ 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
 - Recanalised umbilical vein
 - ✓ **FibroScan** liver stiffness measurement >15 kPa without other explanation
 - ✓ Fibrosis score > stage 4 on **liver biopsy**
- ✓ **Small OV diagnosed within 3 months** defined as:
 - ≤5 mm in diameter, or
 - disappear on moderate insufflation
- ✓ Not received a beta-blocker in the last week
- ✓ 18 years and over
- ✓ Capacity to provide informed consent

- ✗ Non-cirrhotic portal hypertension
- ✗ Current or history of medium/large OV
- ✗ Isolated gastric, duodenal, rectal varices with or without recent bleeding
- ✗ Red signs during gastroscopy, previous variceal haemorrhage
- ✗ Known intolerance / contraindications to beta-blocker use
- ✗ Already receiving a beta-blocker that cannot be discontinued
- ✗ Child Pugh C cirrhosis
- ✗ 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
- ✗ CTIMP in last 3 months



BOPPP Flow Chart



Trial procedures	Pre-screening	Screening Visit	Baseline	Week1 (+/-) 3 days	Week6 (+/-) 2 weeks	Month6 (+/-) 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											
Randomisation			X										
Demographics*		X											
Medical History*		X											
Targeted physical exam*		X				X	X	X	X	X	X		
Weight / Height*		X				X	X	X	X	X	X		
Vital signs (BP/HR)*		X	X	X		X	X	X	X	X	X	X	X
TE/APRI*	X												
FBC*			X			X	X	X	X	X	X	X	
INR*			X			X	X	X	X	X	X	X	
Liver, Renal and Bone profile*			X			X	X	X	X	X	X	X	
IMP dispensing			X			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)	
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		
Adherence to IMP				X		X	X	X	X	X	X	X	
Nurse telephone call					X								

Pilot 1:

Recruitment and Retention

- 12 months following opening of recruitment
- Go / No Go criteria:
 - 8 sites opened
 - 1 patient recruited at each
 - Randomised 80+
 - Retention rate 70%

Pilot 2:

Variceal bleed rate

- Month 30 (June 2022)
- Using Control arm only
- Bleed rate must be $\geq 4\%$
- Sample size 360
- Go / No Go criteria:
 - $\geq 4\%$ continue as planned
 - 2-4% consider trial length or sample size
 - $< 2\%$ stop trial

1) Recruitment barriers / enablers:

- Trial participants that consent, and those that decline:
 - Screening & Consent
 - Trial schedule
 - Acceptability of randomisation
 - Benefits and risks of participation
- Endoscopists, research nurses, pharmacists at sites:
 - Recruitment procedures
 - Support strategies to optimise recruitment
- Variety of sites to reflect UK wide experience and views

2) Treatment implementation post trial

- REC meeting ☒ REC approval ☒
- MHRA submission ☒ CTA approval ☒
- NIHR portfolio adoption ☒ HRA approval ☒
- IMP and placebo manufacture ☒ - shipping to sites May 2019
- Trial Steering and Data Monitoring Committees ☒ Joint meeting 24/04/19
- **Site opening:** June 2019 -> April 2020
- **Pan-London Investigator Meeting:** 24th May 2019
- **First patient first visit** June 2019
- **Pilot phase 1:** Recruitment and Retention - March 2020
- **Pilot phase 2:** Estimation of variceal bleeding rate - June 2022

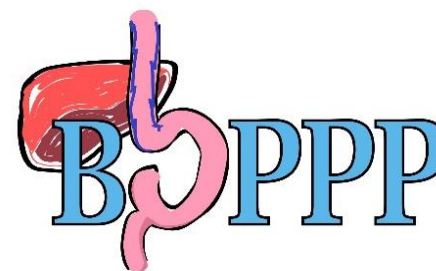
- 36 sites expressed interest – all REC approved
- All provided feasibility information:
 - Experience
 - Resource: local support, Clinical Research Network (CRN) support
 - Estimated patient numbers (screening → eligible → consent)
 - Local clinical pathway compatibility
 - Identifiable issues and challenges
 - Most sites are CALIBRE +ive
- Ranked, TMG division into two waves
 - Wave 1 – opening May 2019 to April 2020
 - Wave 2 – contingency sites (replace closed / unopened)
- Wave 1 officially invited February 2019
 - R&D and Pharmacy packs provided March 2019
 - Internal approvals underway

BOPPP: Site opening

	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11
	May '19	June '19	July '19	Aug '19	Sept '19	Oct '19	Nov '19
KCH & PRUH							
Frimley							
St George's							
Portsmouth							
Brighton							
Bristol							
Nottingham							
Derby							
Plymouth							
Devon & Exeter							
Belfast							
Imperial							
Royal Free							
Barts							
Birmingham							
Newcastle							
Cambridge							
Bradford							
Glasgow							
Liverpool							



- NSBB vs EBL
- 2,600 pts with medium-large OV
- 30 UK sites
- 6 year study



- NSBB vs placebo
- 1,200 pts with small OV
- 20 UK sites
- 6 year study

- CALIBRE and BOPPP are complimentary, not competitive
- If BOPPP pts progress: unblind: *if placebo* → SoC → for CALIBRE
- Joint 1 page information sheet for both trials

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North Bristol NHS Foundation Trust	Dr Zeino Zeino
Addenbrookes Hospital, Cambridge	Dr Jo Leithead
Royal Devon and Exeter Hospital	Dr Andrew Austin
Devon & Exteter	Dr Ben Hudson
Frimley Park Hospital	Dr Kuldeep Cheent
Glasgow Royal Infirmary	Prof Adrian Stanley
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Royal Liverpool University Hospital	Dr Imran Patanwala
Newcastle	Dr Steven Masson
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British Association for the Study of the Liver

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