BASL Annual Meeting
18th September 2019

CALIBRE Trial.

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Honorary Reader

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UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

NHS University Hospitals Birmingham NHS Foundation Trust

NHS National Institute for Health Research

BASL 2019 British Association for the Study of the Liver Incl BLTG Transplant Meeting and BLNA Nurse Meeting
Technology & Innovation Centre, University of Strathclyde, Glasgow, 17-20 September 2019

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Disclosures

- None

Background

- Variceal bleeding accounts for 11% admissions with a GI Bleed in the UK with 4 week mortality 15%
- 50% of all cirrhotic patients have varices
- Prevention of variceal bleeding is an important clinical goal
- Recent UK guidelines have fuelled the debate about optimal therapy for primary prevention

Jairath et al, 2014, Tripathi 2015, NICE 2016

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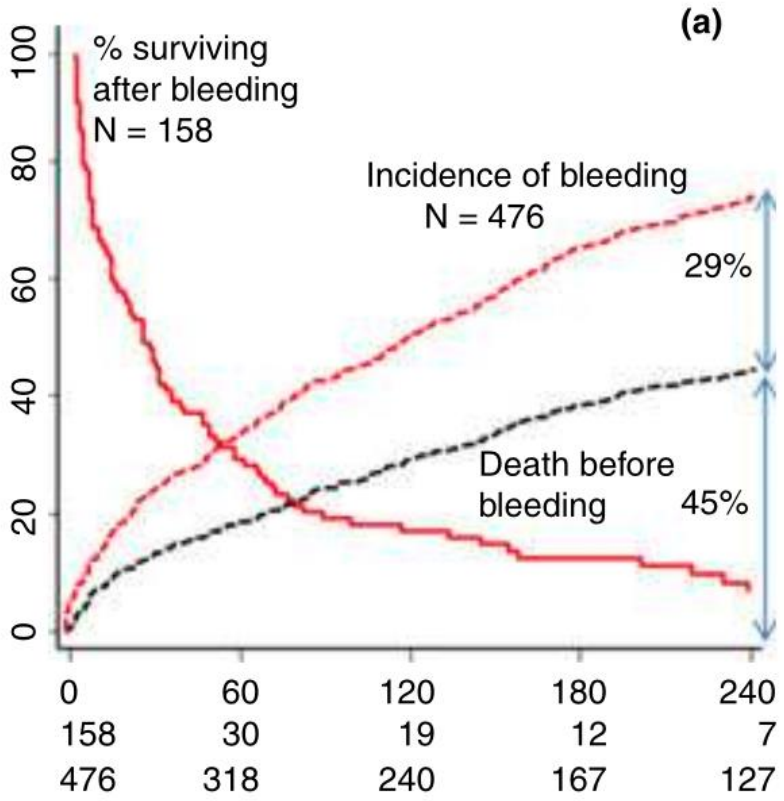
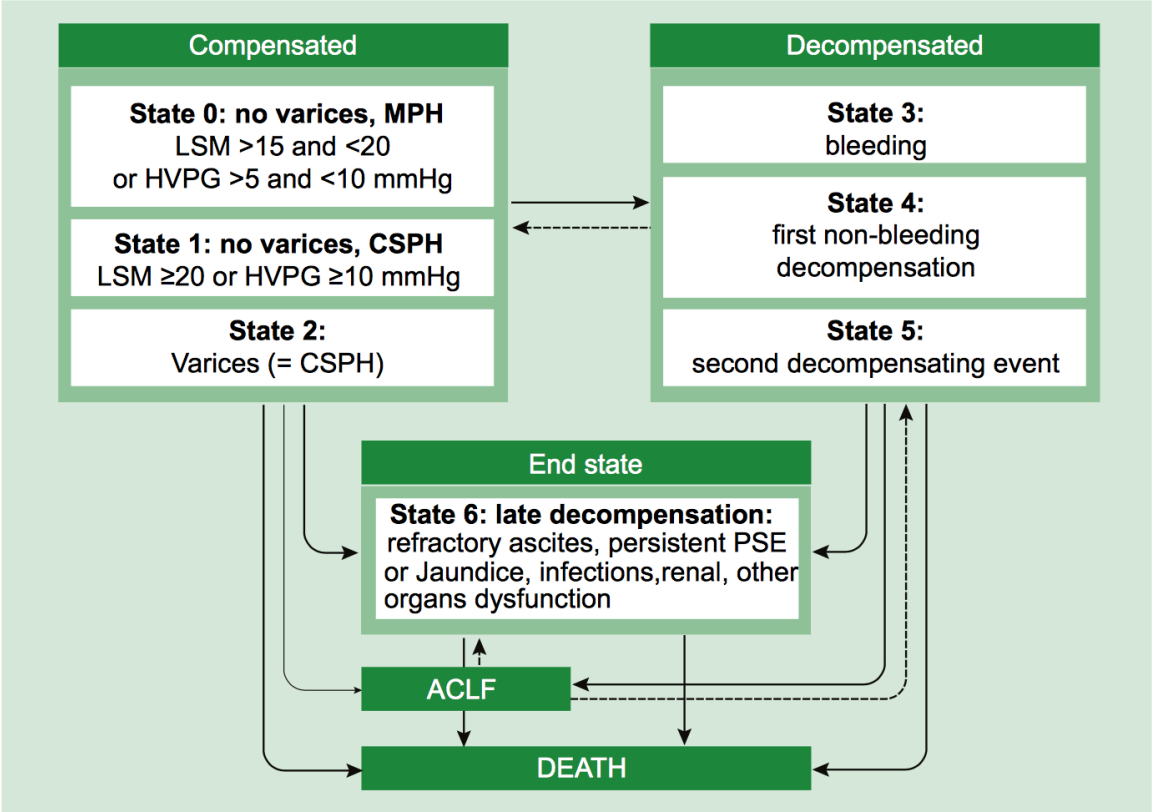
Variceal bleeding is an important landmark in the natural history of cirrhosis





D'Amico et al, 2014, D'Amico et al 2018

Prevention of variceal bleeding is an important clinical goal

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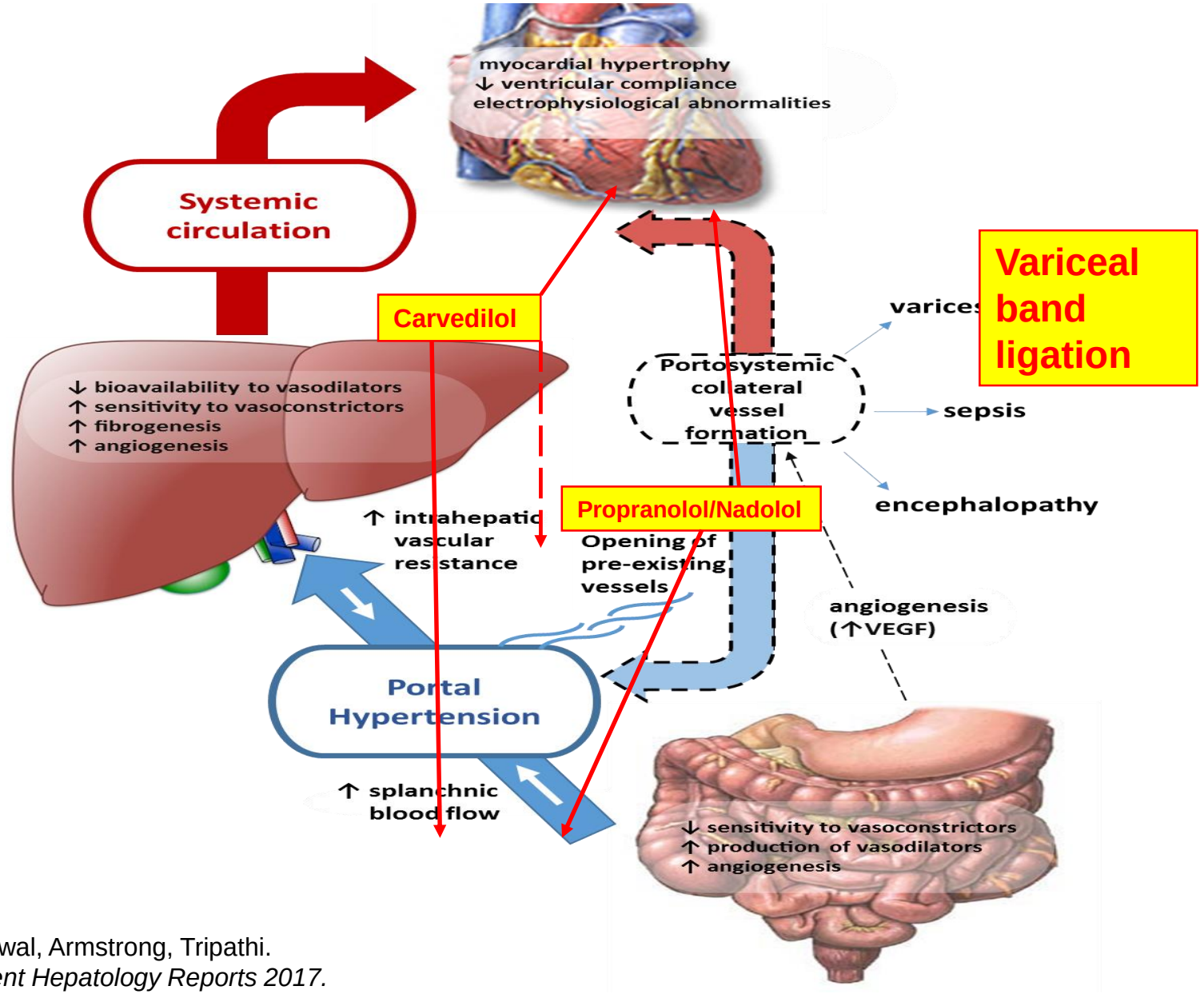
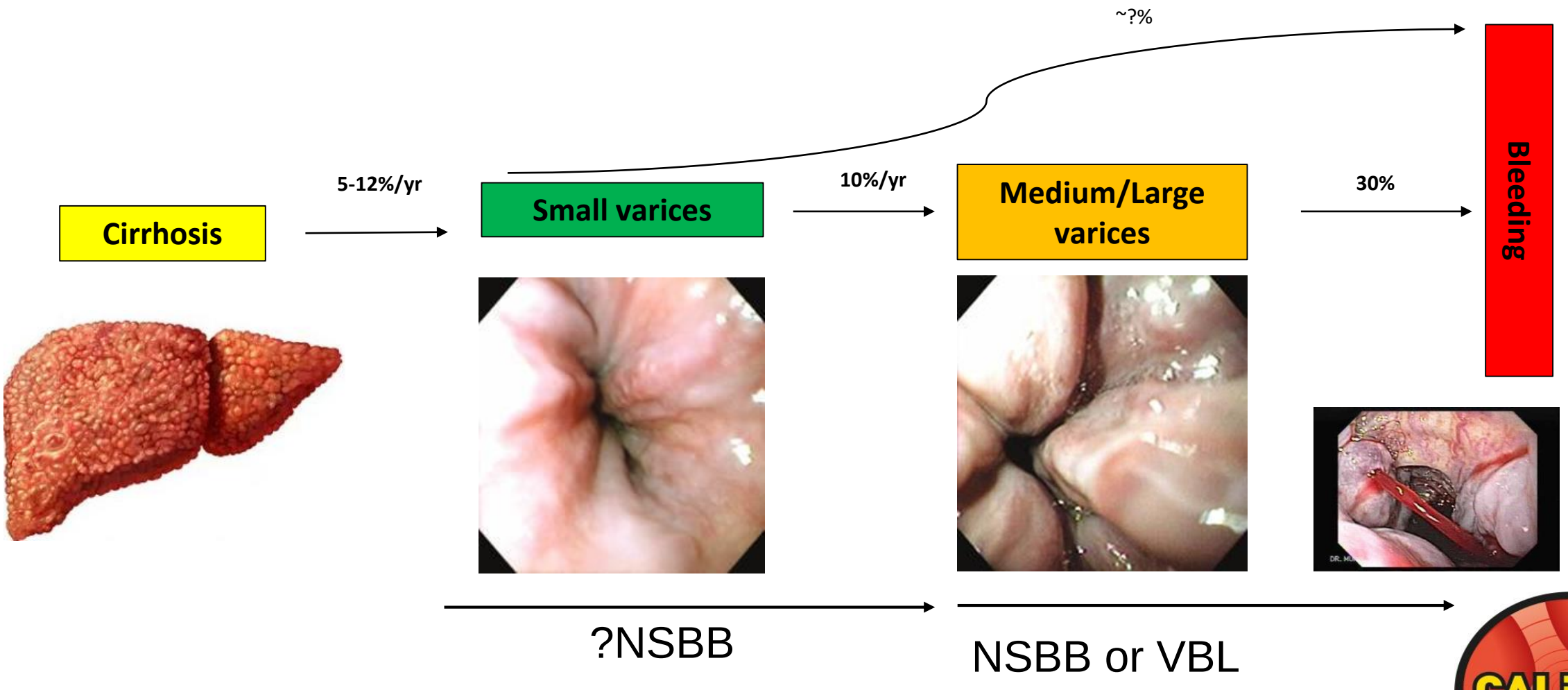
Pathogenesis of portal hypertension



Dhaliwal, Armstrong, Tripathi.
Current Hepatology Reports 2017.

Natural history of varices



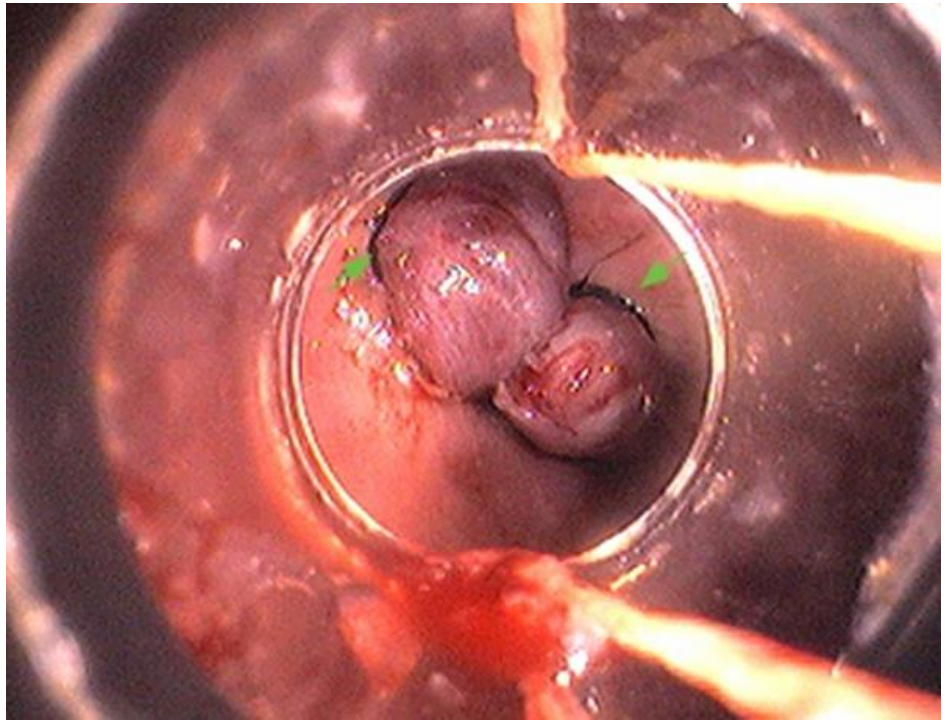
Cales 1988, Merli 2003, Merkel 2004 Groszmann 2005, Bosch 2010, D'Amico 2014, Tripathi 2015, Villanueva 2019

Non-selective beta-blockers

	PROPANOLOL, NADOLOL	CARVEDILOL
PROPOSED MECHANISM OF ACTION	β-1 activity to reduce cardiac output and reduce portal blood flow through splanchnic vasoconstriction via β-2 blockade. 1/3 respond haemodynamically	x2-4 greater beta-blocking action of propranolol Additional intrinsic α1-adrenergic activity. Greater portal hypotensive effect than propranolol (Banares, Hepatol 2002; Sinagra APT 2014) 2/3 respond haemodynamically. Effective in propranolol non-responders
SIDE EFFFECTS/ CAUTIONS	Hypotension, bradycardia, caution in peripheral vascular disease/asthma **To be discontinued at time of SBP, renal impairment and hypotension?**	
INDICATIONS	1^{y} prophylaxis in grade II or larger varices. With VBL for 2^{y} prevention.	
DOSE	Propranolol: 40mg BD, titrated up if tolerated or once HR < 50-55bpm Nadolol: 40mg OD (maximum dose 240mg) or once HR < 50-55bpm	12.5mg OD if tolerated (HR < 50-55bpm, SBP < 90 mmHg)

Reiberger, Gut 2012, Rajoriya, Tripathi, WJP 2016

Variceal band ligation (VBL)



- VBL: reduced local complication over sclerotherapy and better outcomes
- Compared with placebo 64% reduction in variceal bleeding and 45% reduction in mortality (Imperiale, Hepatol 2001)
- Technique very important with multibanders.
- Not for small varices

Primary prevention of variceal bleeding
Medium to large varices

- Offer endoscopic variceal band ligation for the primary prevention of bleeding for people with cirrhosis who have medium to large oesophageal varices.

NICE Guidelines 2016

- We recommend non-cardioselective β blockers (NSBB) or variceal band ligation (VBL). We suggest pharmacological treatment with propranolol as first line. VBL is offered if there are contraindications to NSBB. The choice of VBL or NSBB should also take into account patient choice (level 1a, grade A).
- We suggest carvedilol or nadolol as alternatives to propranolol (level 1b, grade A).

BSG Guidelines 2015

- Either NSBB or endoscopic band ligation (EBL) is recommended for the prevention of the first variceal bleeding of medium or large varices (1a;A).
- The choice of treatment should be based on local resources and expertise, patient preference and characteristics, contra-indications and adverse events (5;D).
- Traditional NSBB (propranolol, nadolol) (1a;A) and carvedilol (1b; A) are valid first line treatments.

Baveno 6 (2015)

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Small varices

- The evidence updates for this guideline confirm that the evidence on which to base recommendations for use of NSBBs for small varices is limited and warrants further research

NICE Guidelines 2016

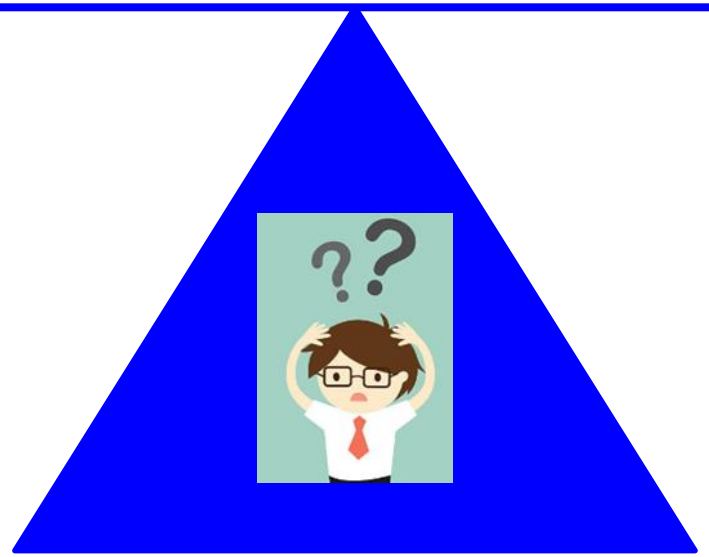
- If grade I varices and red signs or grade 2–3 varices are diagnosed, we recommend that patients have primary prophylaxis irrespective of the severity of the liver disease (level 1a, grade A).

BSG Guidelines 2015

Primary prevention in medium/large varices - UK Guidelines Conundrum

NICE 2016:
Use VBL as first line

BSG 2015:
Recommends VBL and NSBB (propranolol (nadolol/carvedilol)) and suggests NSBB as first line. VBL if contraindications of NSBB



NICE 2016, Tripathi 2015

Health Technology Assessment Programme

NHS National Institute for Health Research

HTA no 16/99

Primary prevention of variceal bleeding in patients with liver cirrhosis

Introduction

The aim of the HTA Programme is to ensure that high quality research information on the effectiveness, costs and broader impact of health technology is produced in the most efficient way for those who use, manage, provide care in or develop policy for the NHS. Topics for research are identified and prioritised to meet the needs of the NHS. Health technology assessment forms a substantial portfolio of work within the National Institute for Health Research and each year about fifty new studies are commissioned to help answer questions of direct importance to the NHS. The studies include both primary research and evidence synthesis.

Research Question:

What is the clinical and cost effectiveness of non-selective beta-blockers compared to endoscopic variceal band ligation for primary prevention of variceal bleeding?

1. **Intervention:** Oral non-selective beta-blockers (NSBB), choice to be justified by applicants.
2. **Patient group:** Adults with cirrhosis and medium or large oesophageal varices, no history of variceal haemorrhage and no contraindications to beta blocker use.
3. **Setting:** Secondary care.
4. **Control:** Endoscopic variceal band ligation (VBL).
5. **Study design:** A randomised non inferiority trial to compare NSBB against VBL. When appropriate subgroup analyses should be performed. The trial data should also be incorporated into a new or updated systematic review with meta-analyses. A model of cost effectiveness is required.
6. **Important outcomes:** Time to first variceal bleeding event; overall mortality.
   Other outcomes: Adverse effects; an updated meta-analysis; patient preference; QoL; cost effectiveness.
7. **Minimum duration of follow-up:** Duration of study sufficient to accumulate enough events to inform the model.

Trial Design	• A multicentre randomised controlled, open-label, self-evident two-arm trial with internal pilot.
Aim	• To investigate the clinical and cost-effectiveness of carvedilol versus variceal band ligation in patients with cirrhosis and medium to large oesophageal varices that have not bled
Sample size 2630 - CALIBRE largest ever Phase III trial in cirrhosis	• Based on superiority hypothesis – 33% proportional difference in 1 year bleeding with carvedilol (absolute 12% (VBL), 8% (carvedilol))
NIHR HTA funded - £2.3m	• Sponsor University of Birmingham • Over 75 months
Recruitment over 4 years nationally	• All acute NHS trusts and health boards in UK potentially eligible
Primary end point	• Any variceal bleeding within 1 year of randomisation

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BMJ Open Gastroenterology

Study protocol for a randomised controlled trial of carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE trial)

Dhiraj Tripathi,[1,2] Peter Hayes,[3] Paul Richardson,[4] Ian Rowe,[5] James Walter Fersuon,[1,2] Peter Devine,[6] Jonathan Mathers,[7] Christopher Poyner,[7] Sue Jowett,[7] Kelly Handley,[8] Margaret Grant,[8] Gemma Slinn,[8] Peter Brocklehurst,[8] Khaled Ahmed,[8] on behalf of CALIBRE trial collaborative group

To cite: Tripathi D, Hayes P, Richardson P, *et al*. Study protocol for a randomised controlled trial of carvedilol versus variceal band ligation in primary prevention of variceal bleeding in

ABSTRACT

Introduction Liver cirrhosis is the fifth largest cause of adult deaths, and a major complication, variceal bleeding is associated with a 1-year mortality of 40%. There is uncertainty on the first-line therapy for prevention of variceal bleeding owing to a lack of adequately powered

hypertension and variceal bleeding. In patients with cirrhosis, varices develop at a rate of 5% per year with 10 year cumulative incidence of 44%.[3] At least 3000 patients are admitted to hospital in England per year with variceal bleeding, with inpatient mortality

Inclusion criteria (revised)

- Liver cirrhosis as defined clinically, radiologically, with transient elastography (where liver stiffness in the clinician's opinion supports a diagnosis of cirrhosis) or on histology.
- Already on selective beta-blockers that can be discontinued (at clinician's discretion)
- Medium and/ or large varices that have never bled as defined in the BSG guidelines.

Exclusion criteria (revised)

- Age < 18 years.
- Pregnant or lactating women .
- Known intolerance or contraindications to beta-blockers including asthma.
- Current or past history of non-selective beta blocker use (such as carvedilol, nadolol or propranolol)
- Current or history of variceal banding ligation.
- Presence of malignancy or systemic disease that significantly affects one-year survival.
- Unable to give informed consent.
- Acute alcoholic hepatitis.
- Patients with surgical or radiological porto-systemic shunts such as transjugular portosystemic stent-shunt (TIPSS).
- Previous organ transplantation

Primary outcome:

- Any variceal bleeding within one year of randomisation

Secondary outcomes:

- Time to first variceal bleed in days from randomisation
- Mortality at one year (from randomisation):
  - All-cause mortality
  - Liver related mortality
  - Cardiovascular mortality
- Transplant free survival at one year (from randomisation)
- Adverse events related to treatment (up to 12 months after randomisation):
  - Dysphagia
  - Symptomatic hypotension
  - Dyspnoea
  - Gastrointestinal upset
- Other complications of cirrhosis:
  - New onset ascites
  - New onset encephalopathy
  - Spontaneous bacterial peritonitis
  - Hepatocellular carcinoma
  - Any renal dysfunction
- Health-related quality of life (EQ-5D-5L) from randomisation to six and 12 months.
- Use of healthcare resources, costs and cost-effectiveness
- Patient preference (qualitative sub study)
- Use of alternative therapies.
- Crossover therapies.

Carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE)

Inclusion criteria

1. Liver cirrhosis as defined clinically, radiologically, with transient elastography (where liver stiffness in the clinician's opinion supports a diagnosis of cirrhosis) or on histology.
2. Already on selective beta-blockers that can be discontinued (at clinician's discretion).
3. Medium and/ or large varices that have never bled as defined in the BSG guidelines [1]

Exclusion criteria

1. Age < 18 years.
2. Pregnant or lactating women.
3. Known intolerance or contraindications to beta-blockers including asthma.
4. Current or past history of non-selective beta blocker use (such as carvedilol, nadolol or propranolol)
5. Current or history of variceal banding ligation.
6. Presence of malignancy or systemic disease that significantly affects one-year survival.
7. Unable to give informed consent.
8. Acute alcoholic hepatitis.
9. Patients with surgical or radiological porto-systemic shunts such as transjugular portosystemic stent-shunt (TIPSS).
10. Previous organ transplantation.

Obtain informed consent

Confirm by endoscopy

Qualitative study – those consented to participate and decliners.

Randomisation

Variceal band ligation per BSG guidelines[1]

Varices are banded at 2–4-weekly intervals until eradication. After successful eradication of the varices, repeat endoscopy as per local protocols. Any recurrent varices should be treated with further VBL until eradication.

Carvedilol 12.5 mg od

Follow-up:
4 weeks

Adverse events

Follow-up:
6 months
12 months

- Primary outcome: Proportion of patients experiencing variceal bleeding within 1 year of randomisation
- Hepatocellular carcinoma surveillance per standard care
- Variceal band ligation per standard care

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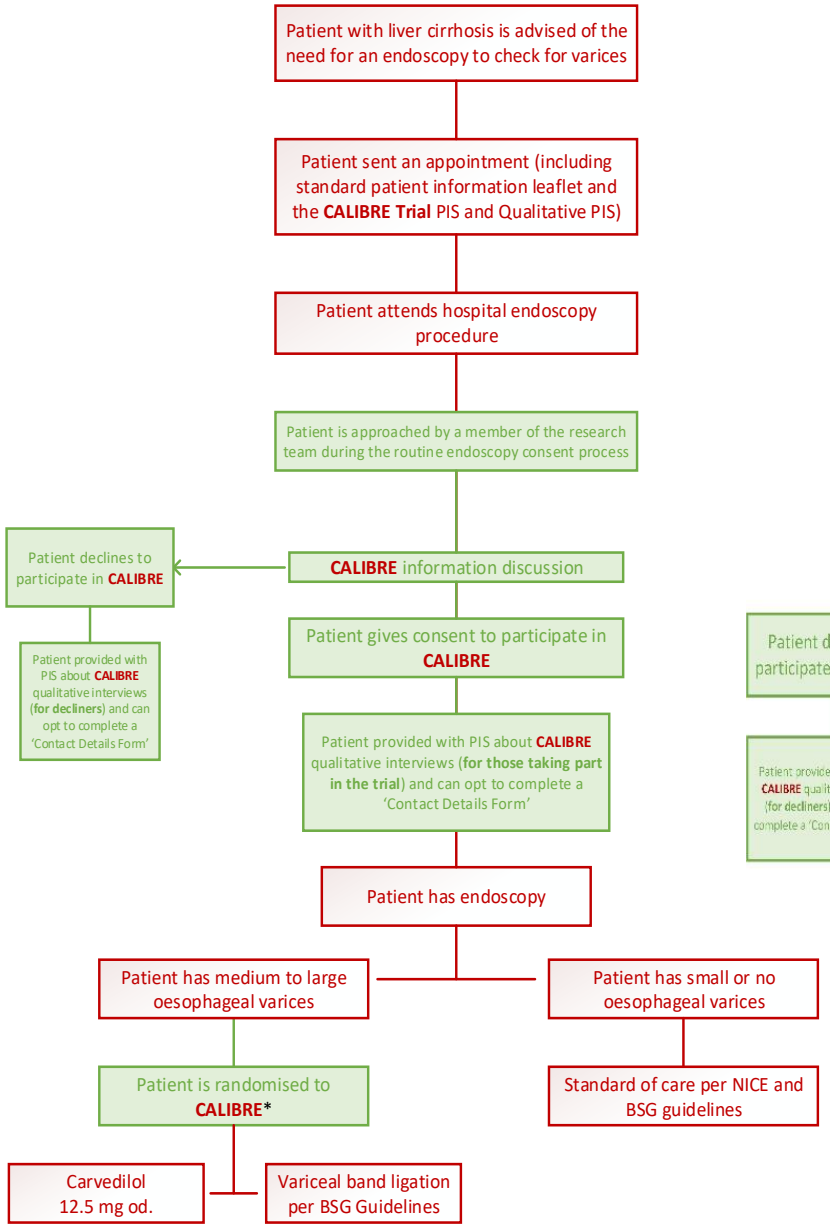
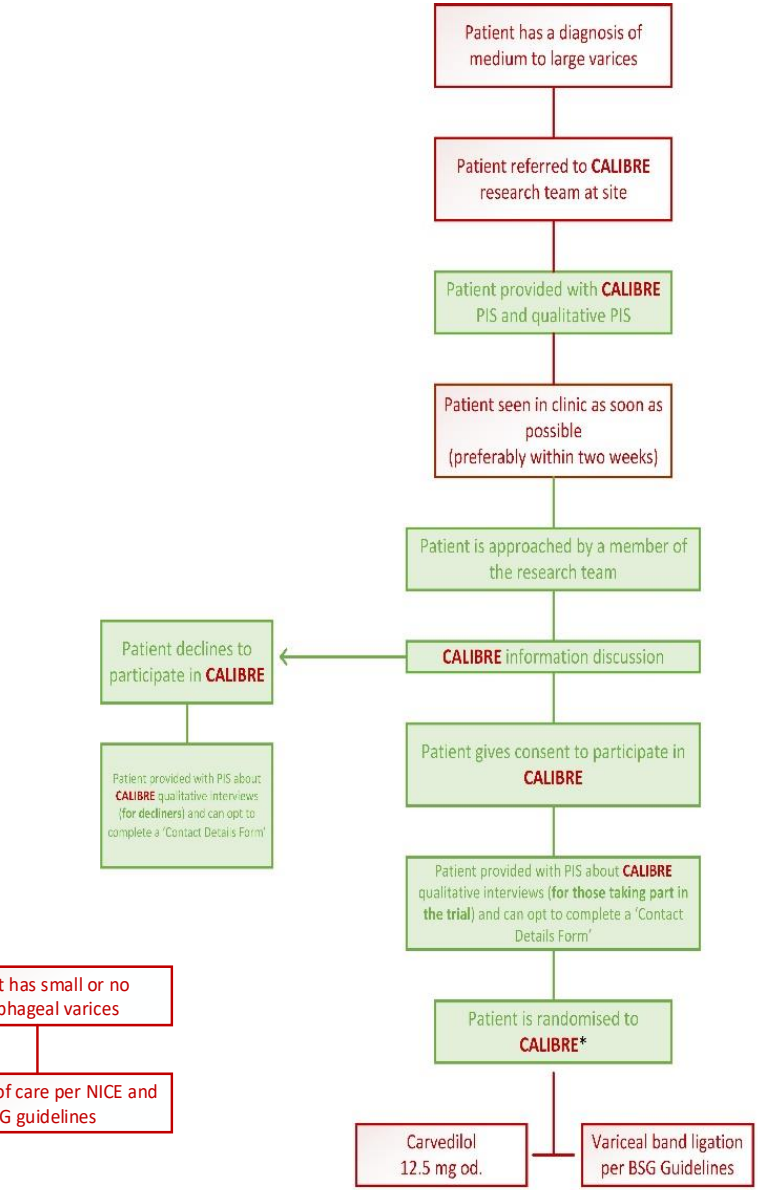
Consent pathways



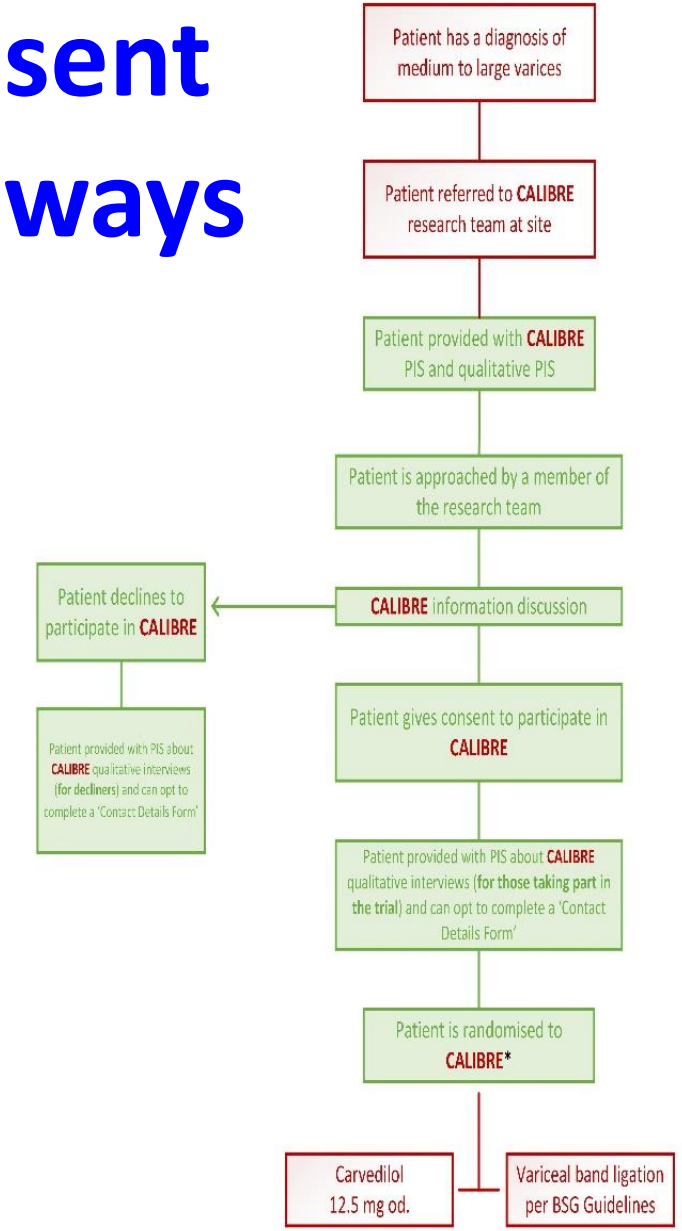
**If patient is not eligible to be randomised into CALIBRE or declines to participate, then treat as per standard of care (refer to NICE and BSG guidelines and/ or local policies).*



**If patient is not eligible to be randomised into CALIBRE or declines to participate then treat as per standard of care (refer to NICE and BSG guidelines and/ or local policies).*

Standard of care

Research activity



**If patient is not eligible to be randomised into CALIBRE or declines to participate then treat as per standard of care (refer to NICE and BSG guidelines and/ or local policies).*

Standard of care

Research activity

CALIBRE Progress – Jan 2019 - present

40 sites are now live

- 8th Month of pilot
- 59 sites have now been contacted
- 48 SIVs have now been completed
- Projection – 20 sites in 12 months we have opened 40
- 6 more sites opening in the next 2 weeks

NIHR | National Institute for Health Research

CALIBRE Progress – Jan 2019 - present

UHB (PI Dr Neil Rajoria)	Torbay & South Devon (PI Dr James Neale)
Derby (PI Dr Andrew Austin)	Royal Cornwall (PI Dr Syed Hussaini)
Hull (PI Dr Lynsey Corless)	Leeds (PI Dr Mark Adersley)
Edinburgh (PI Prof Peter Hayes)	South Tees (PI Dr Darren Craig)
York (PI Dr John Hutchinson)	Royal Liverpool (PI Dr Imran Patanwala)
Glasgow Royal Infirmary (PI Prof Adrian Stanley)	Gateshead (PI Dr Dina Mansour)
Dundee (PI Dr Michael Miller)	Royal Devon & Exeter (PI Dr Ben Hudson)
Aberdeen (PI Dr Ashis Mukhopadhya)	Durham (PI Dr Francisco Porras-Perez)
Swansea (PI Dr Chin Lye Ch'Ng)	Portsmouth (PI Dr Richard Aspinall)
Scarborough (PI Dr Charles Milson & Dr John Hutchinson)	Plymouth (PI Prof Matthew Cramp)
Aintree-Liverpool (PI Cyril Sieberhagen)	Cambridge (PI Dr Joanna Leithead)
Basildon (PI Dr Gavin Wright)	Guy's & St. Thomas (PI Dr Phillip Berry)
King's College Hospital (PI Dr Brian Hogan)	Shrewsbury and Telford Hospital (PI Dr Ulrich Thalheimer)
Heartlands (PI Dr Andy King)	Royal London (PI Dr Vikram Sharma)
Cardiff (PI Dr Tom Pembrooke)	Sheffield (PI Dr Laura Harrison)
Southampton (PI Dr Janisha Patel)	Coventry (PI Dr Esther Unitt)
Oxford (PI Dr Jeremy Cobbold)	New Cross Wolverhampton (PI Dr Chris Corbett)
Royal Free (PI Dr Raj Mookerjee)	Wigan & Leigh (PI Dr Richard Keld)
Nottingham (PI Dr Stephen Ryder)	South Tynside (PI Dr Joanne Topping)
Bradford (PI Dr Sulleman Moreea)	Newcastle (PI Dr Steven Masson)

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Qualitative update

- Primary aim: To ensure the feasibility and acceptability of the trial and its interventions.
- 30 incliner qualitative interviews complete with 2 follow up complete
- 5 decliner interviews out of 10 complete
- 4 site staff interviews complete a further 6 required

CALIBRE RECRUITMENT – PILOT PHASE

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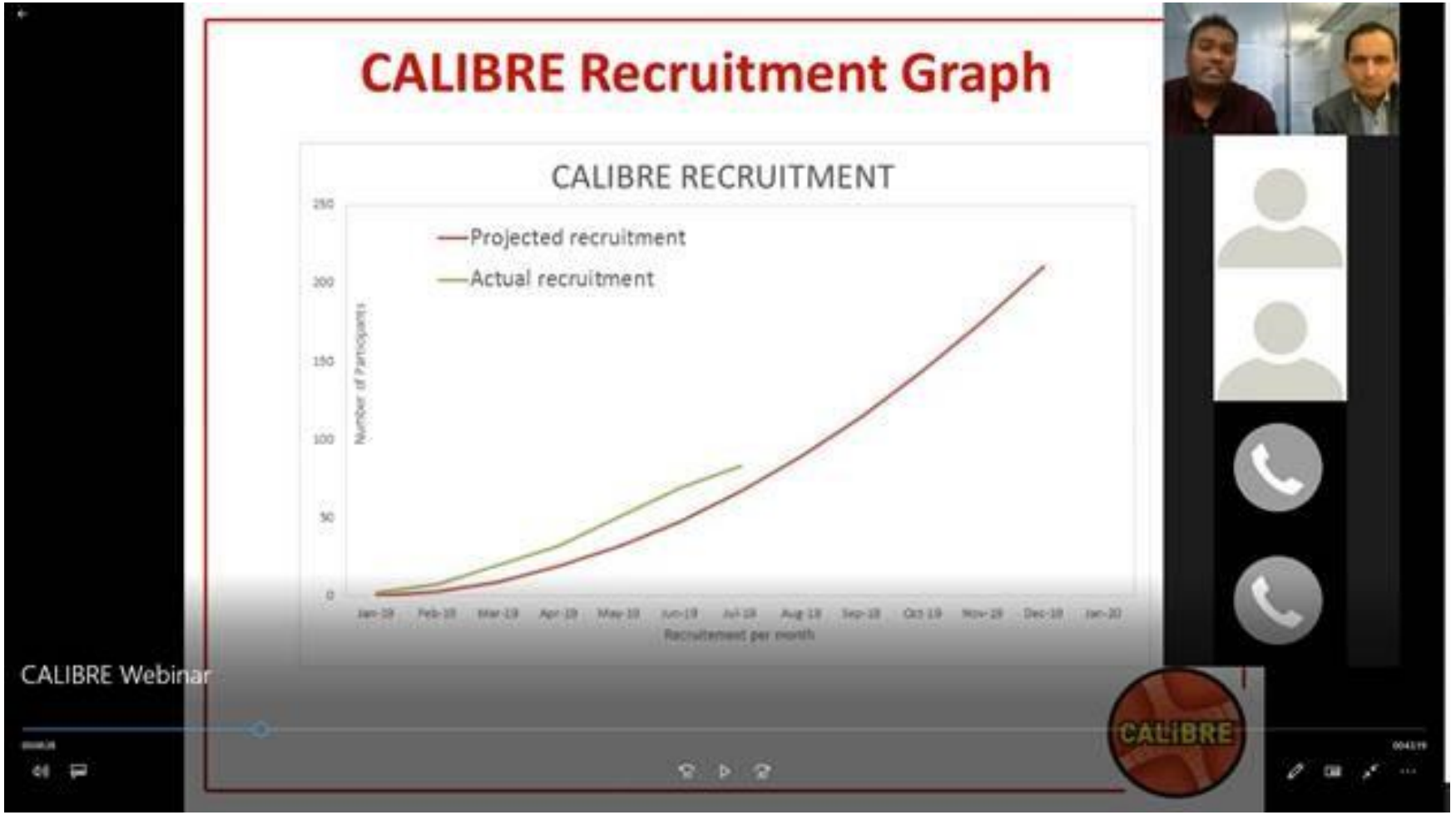

Join our 2nd CALIBRE Webinar on Thursday the 21st November 2019 from 1-2pm
Register here: https://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/portfolio-v/CALIBRE/investigators/meetings.aspx
Link: https://zoom.us/j/907599679
Telephone: Call 02030512874 then input meeting ID 907599679 then #
Location: Room 113

CALIBRE - Carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis

In 'calibre'

- CALIBRE
- Birmingham Clinical Trials Unit (BCTU)
- For Investigators
- Publications
- News and events
- Contact us

Open all sections

Design

Aim of Study

Setting

Target population

Intervention

Measurement of outcomes and costs

NHS National Institute for Health Research

Conclusions

- Prevention of variceal bleeding is an important clinical goal
- Controversy regarding efficacy of banding vs NSBB in primary prevention of medium/large varices.
- CALIBRE aims to provide conclusive evidence in primary prevention in patients with cirrhosis and medium/large varices.

THANK YOU!

CALIBRE TRIAL MANAGEMENT GROUP

Clinical

Dr Dhiraj Tripathi, Birmingham (Chief Investigator)

Dr James Ferguson, Birmingham

Dr Ian Rowe, Leeds

Dr Paul Richardson, Liverpool

Prof Peter C Hayes, Edinburgh

PPI Representative

Mr Peter Devine

BCTU, University of Birmingham (Sponsor)

Prof Peter Brocklehurst (Director)

Dr Margaret Grant (Director of Operations and Trials Management)

Dr Jonathan Mathers, Mr Christopher Poyner (Qualitative research)

Dr Susan Jowett (Health Economics)

Dr Kelly Handley (Medical statistics)

Dr Khaled Ahmed (Senior Trial Manager)

Ms Gemma Slinn (Team leader – trial management)

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