CALIBRE TRIAL

REFRESHER TRAINING SLIDES

(PROTOCOL V3.0 DATED 7TH SEPTEMBER 2021)

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

Chief Investigator: Prof. Dhiraj Tripathi

Trial Manager: Lisa Holden

Sponsor: University of Birmingham

NIHR National Institute for Health Research

twitter @Calibretrial

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

CALIBRE: STUDY DESIGN

Randomised controlled parallel group trial

Open-label

Two interventions:

Carvedilol vs. Variceal Band Ligation

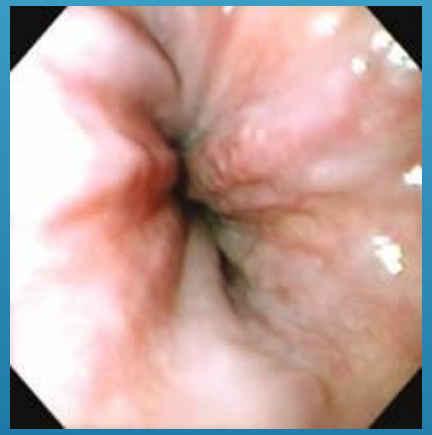
2630 participants

12 month follow-up

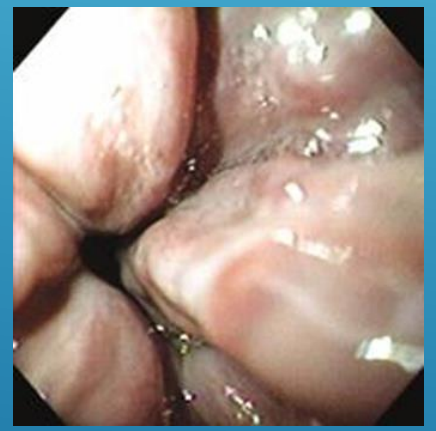
NATURAL HISTORY OF VARICES

~?%

Cirrhosis → (5-12%/yr) → Small varices → (10%/yr) → Medium/Large varices → (30%) → Bleeding



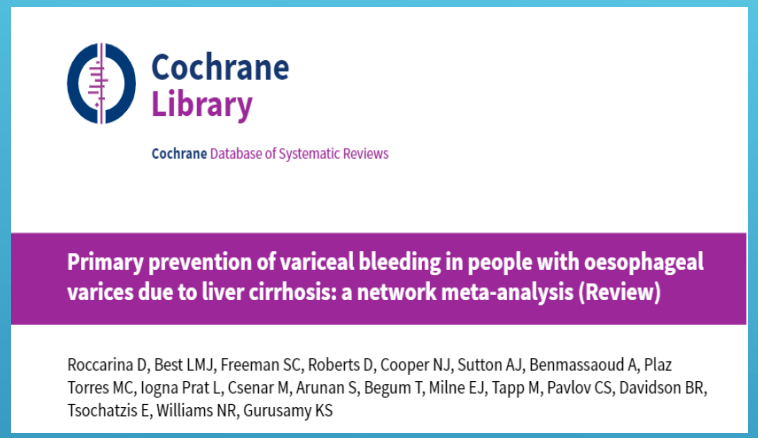
BPPPP



CALIBRE

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

RESEARCH QUESTION



NICE recommends VBL

- **Recent Cochrane network meta-analysis highlights the uncertainty in comparison of VBL vs NSBB in primary prevention of variceal bleeding**
  - 85% of the included trials reported mortality; only about
  - 15% of trials reported serious adverse events adequately
  - 40% of trials reported variceal bleeding adequately
  - <10% of trials described other decompensation events.
  - Too small sample sizes.
  - Did not adhere to the SPIRIT and CONSORT statements and were seldom based on systematic reviews of previous trials.
- **The current ongoing trials may answer most of the uncertainties.**
- **These trials expect to recruit more than 4000 participants by 2024.**

BSG – NSBB and VBL

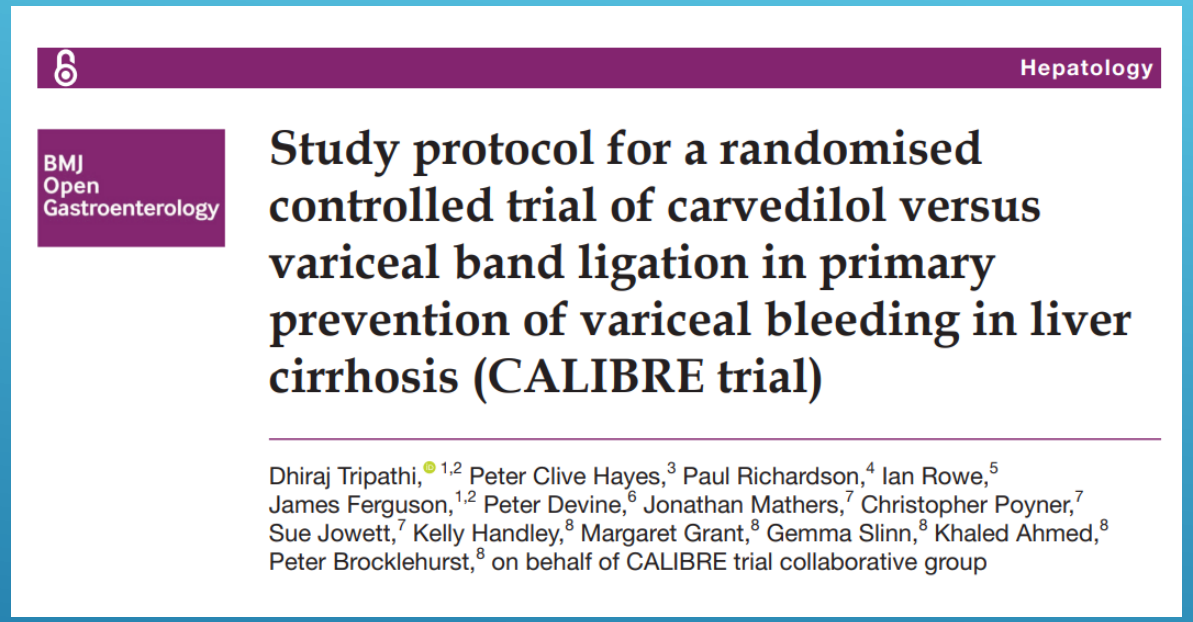
CALIBRE: BSG RESEARCH STRATEGY

Objective 1: Recovery of funded trials following COVID-19 delays. The CRG will facilitate patient recruitment to target nationally funded trials in hepatology 2021-24, including CALIBRE, BOPPP, ASEPTIC, and PROMISE.

COVID-19 RECOVERY

A key priority for the CRG is to support existing studies in achieving continued recruitment into trials, including trials such as CALIBRE and BOPPP as well as the other studies in advanced liver disease.

CALIBRE: PUBLICATIONS



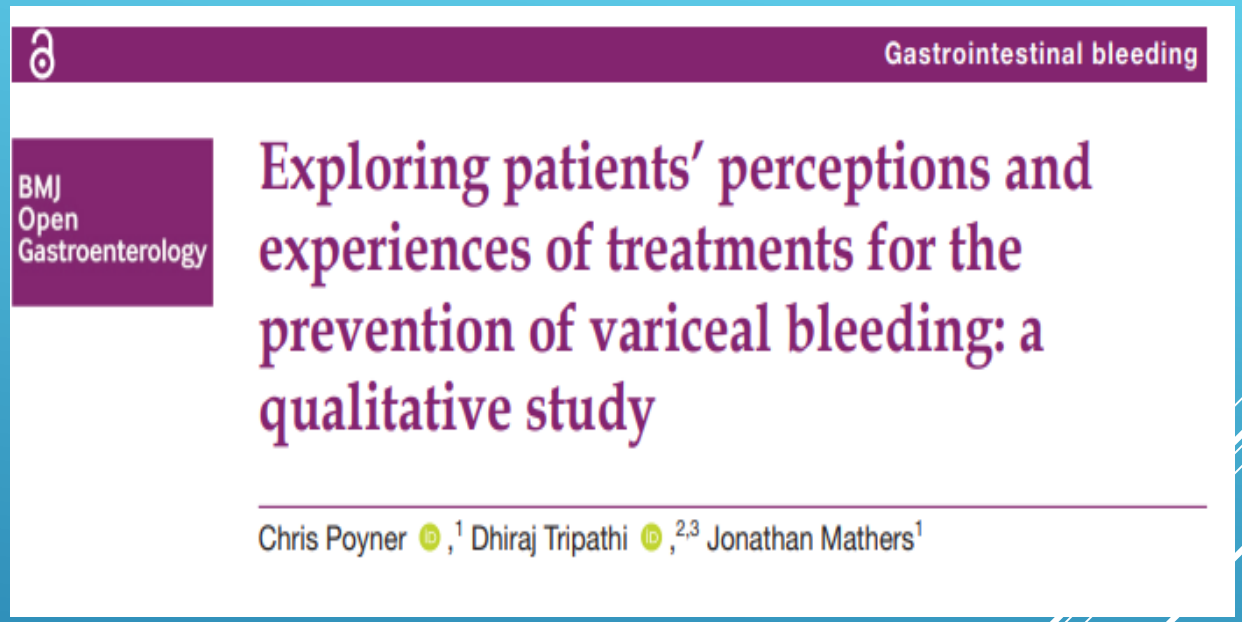
Hepatology

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

BMJ Open Gastro 2019;6:e000290. doi:10.1136/ bmjgast-2019-000290



Gastrointestinal bleeding

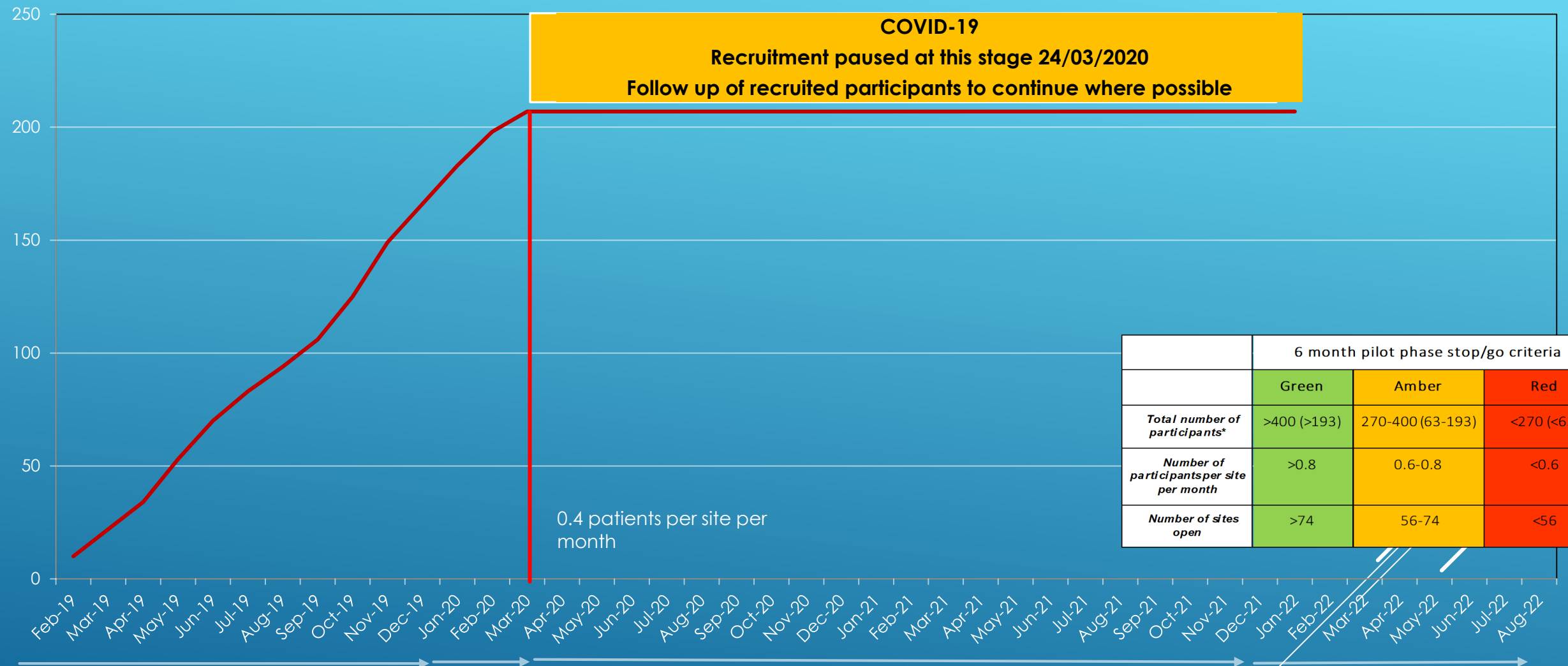
BMJ Open Gastroenterology

Exploring patients' perceptions and experiences of treatments for the prevention of variceal bleeding: a qualitative study

Chris Poyner ,[1] Dhiraj Tripathi ,[2,3] Jonathan Mathers[1]

BMJ Open Gastro 2021;8:e000684. doi:10.1136/ bmjgast-2021-000684

CALIBRE: CURRENT STATUS



	6 month pilot phase stop/go criteria		
	Green	Amber	Red
*Total number of participants**	>400 (>193)	270-400 (63-193)	<270 (<63)
Number of participantsper site per month	>0.8	0.6-0.8	<0.6
Number of sites open	>74	56-74	<56

Pilot phase Jan '19 – Jan '20:
175 participants (250)
55 live sites (20)
0.4 participants per site per month (1.6)

Post pilot to pause :
207 participants
57 live sites

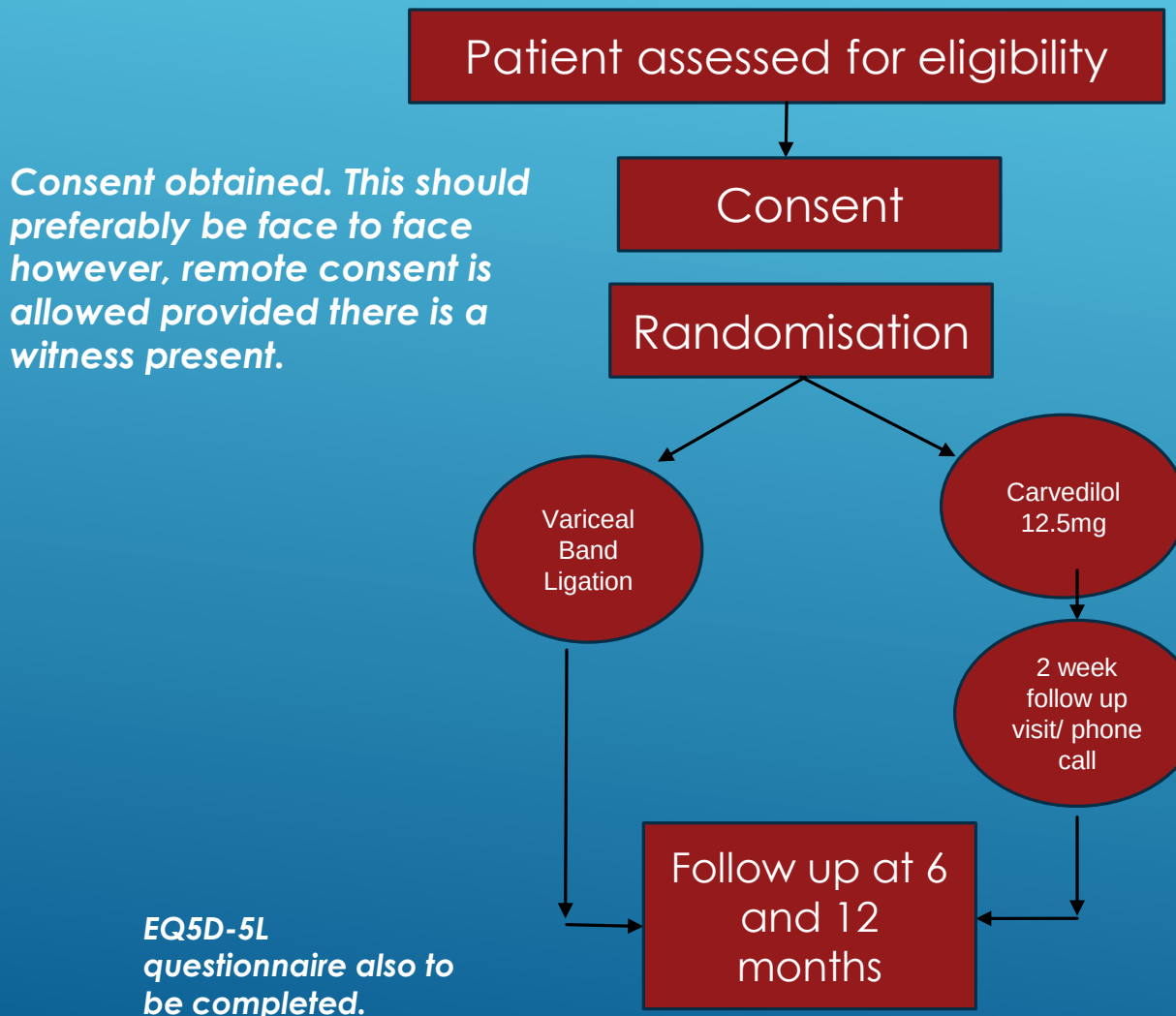
- **To remain paused in light of COVID-19 and impact on endoscopy services.**
- **HTA monitoring meeting – November 2020**
- **Advise to continue to suspend for 6/12**
- **Recovery plan - HTA Monitoring meeting – July 2021**
- **Green light to start process of resuming recruitment September 2021**

Resume recruitment with 6 month pilot

CALIBRE: RECOVERY PLAN

Attract additional sites	• Feasibility assessment ongoing. • Modelling assumes up to 75 sites.
Continued promotion	• CALIBRE has received much attention in national meetings under the auspices of BSG/BASL.
Qualitative study findings	• Insights into patient and clinician perception of CALIBRE and treatment preferences. • Facilitate recruitment e.g. explaining difference between diagnostic vs therapeutic endoscopy, that banding is not surgery, and that sedation is offered.
Training	• Ongoing training for underperforming sites. • Access to online resources – refresher training, webinars.
Associate PI scheme	• CALIBRE is registered with Associate PI scheme.
Communications	• Robust communication with sites (including R&D management), respective CRN delivery managers. • Identify issues early and work towards solutions.
COVID-19	• Pragmatic nature permits data to be collected as part of standard of care. • Remote consultations and remote consent.

CALIBRE: STUDY FLOW CHART



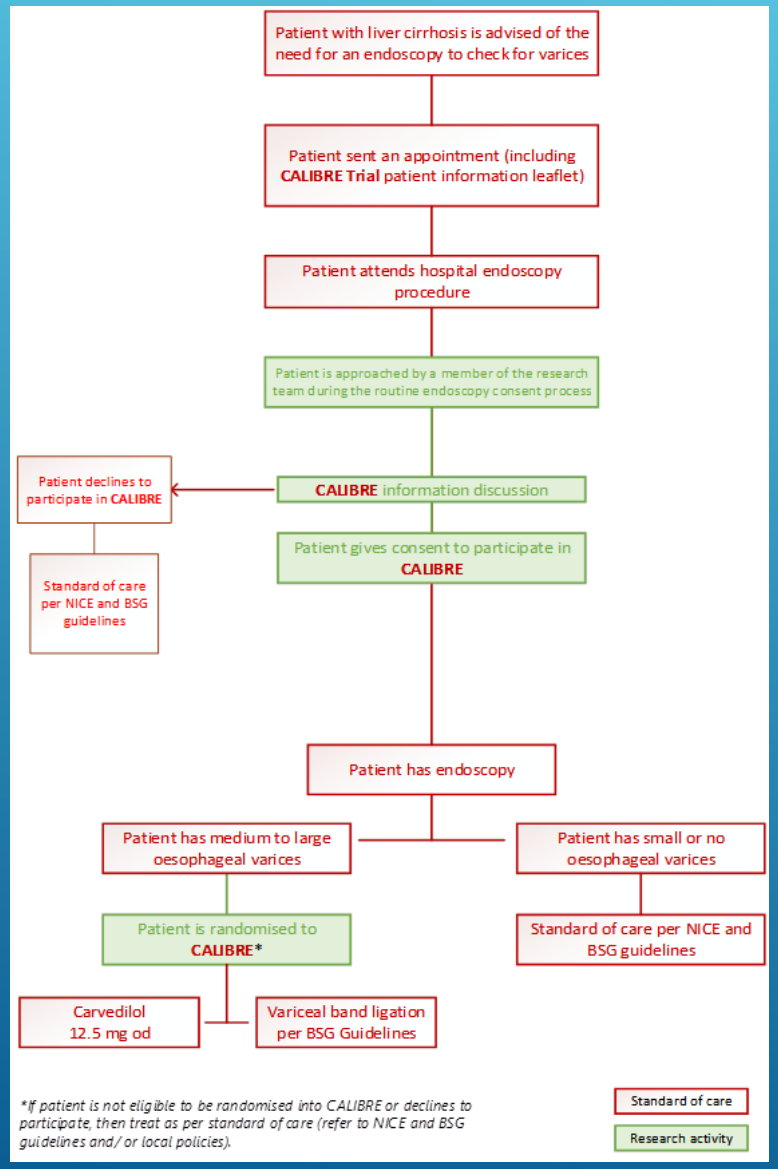
Consent obtained. This should preferably be face to face however, remote consent is allowed provided there is a witness present.

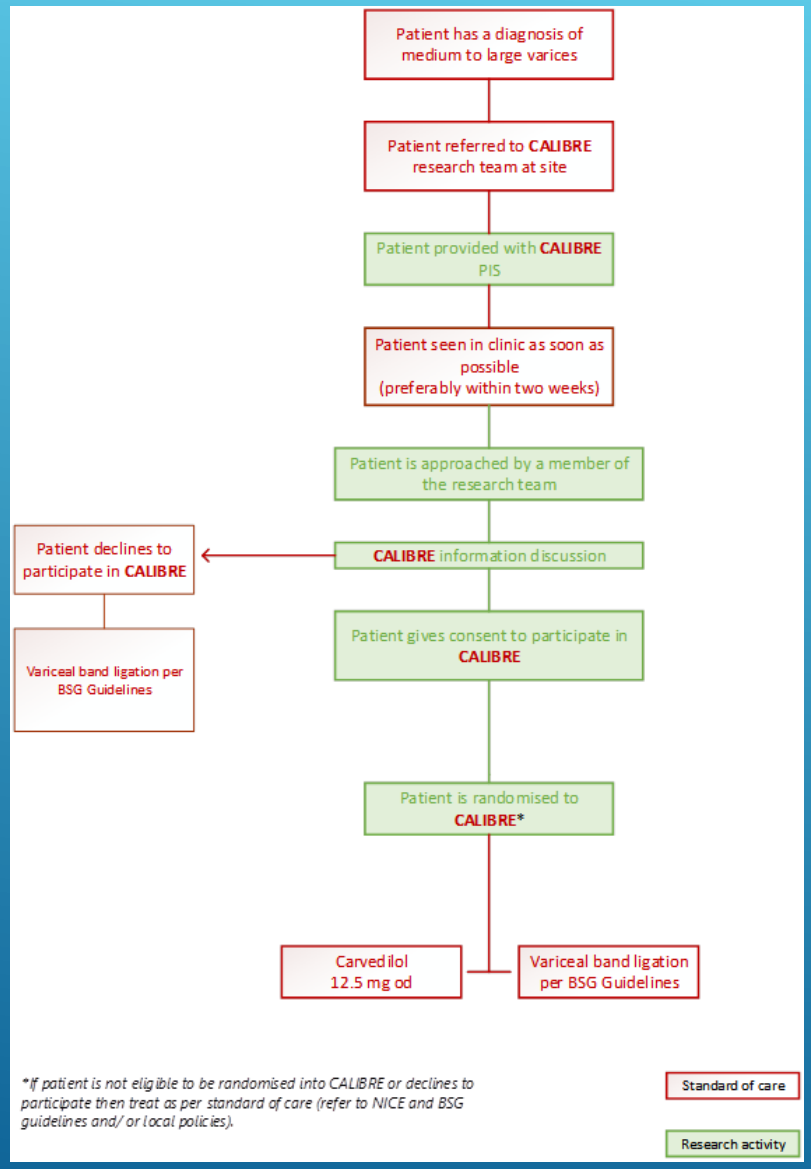
It is important to stress to the patient that banding is NOT surgery and sedation is offered. It is also important to stress that they WILL require one of these treatments whether they enter the trial or not.

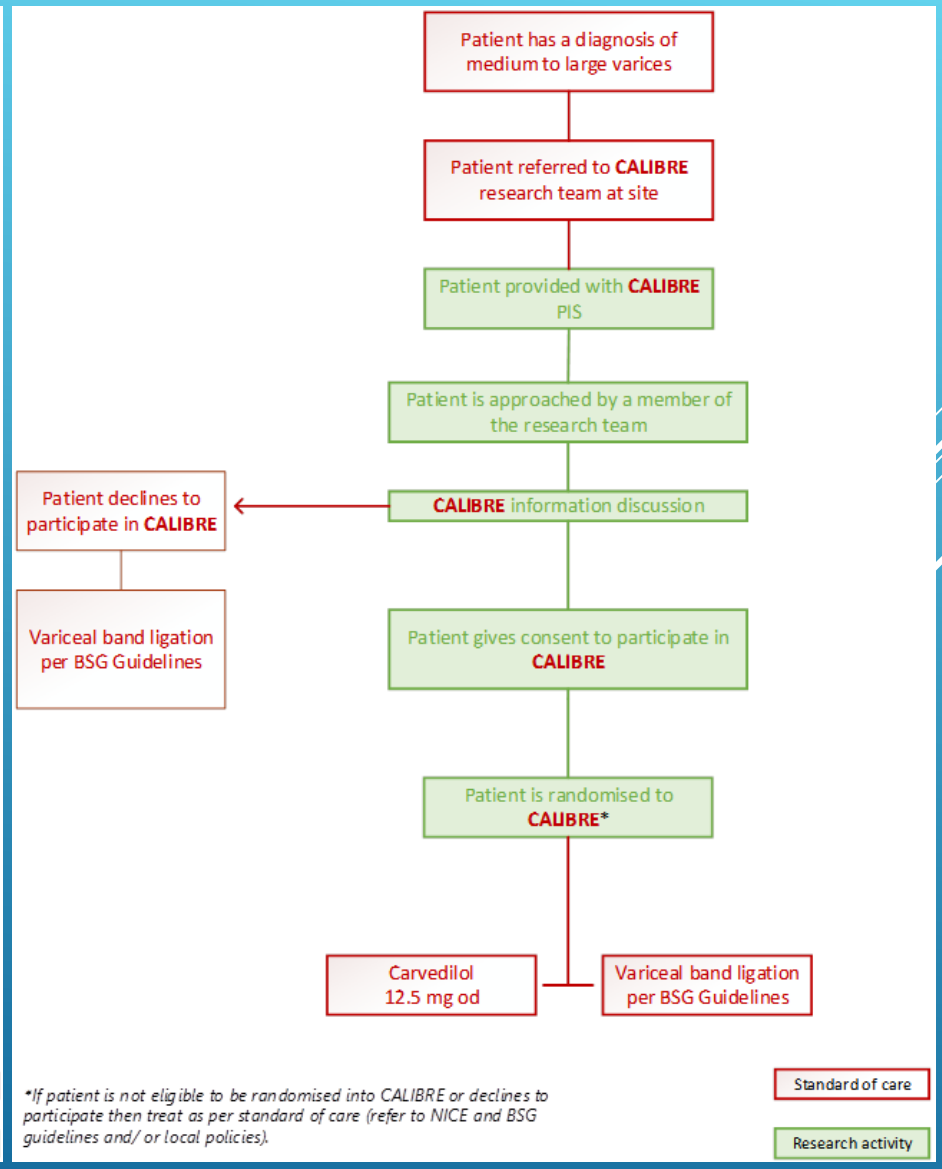
Adverse Events recorded

EQ5D-5L questionnaire also to be completed.

CALIBRE: CONSENT PATHWAYS



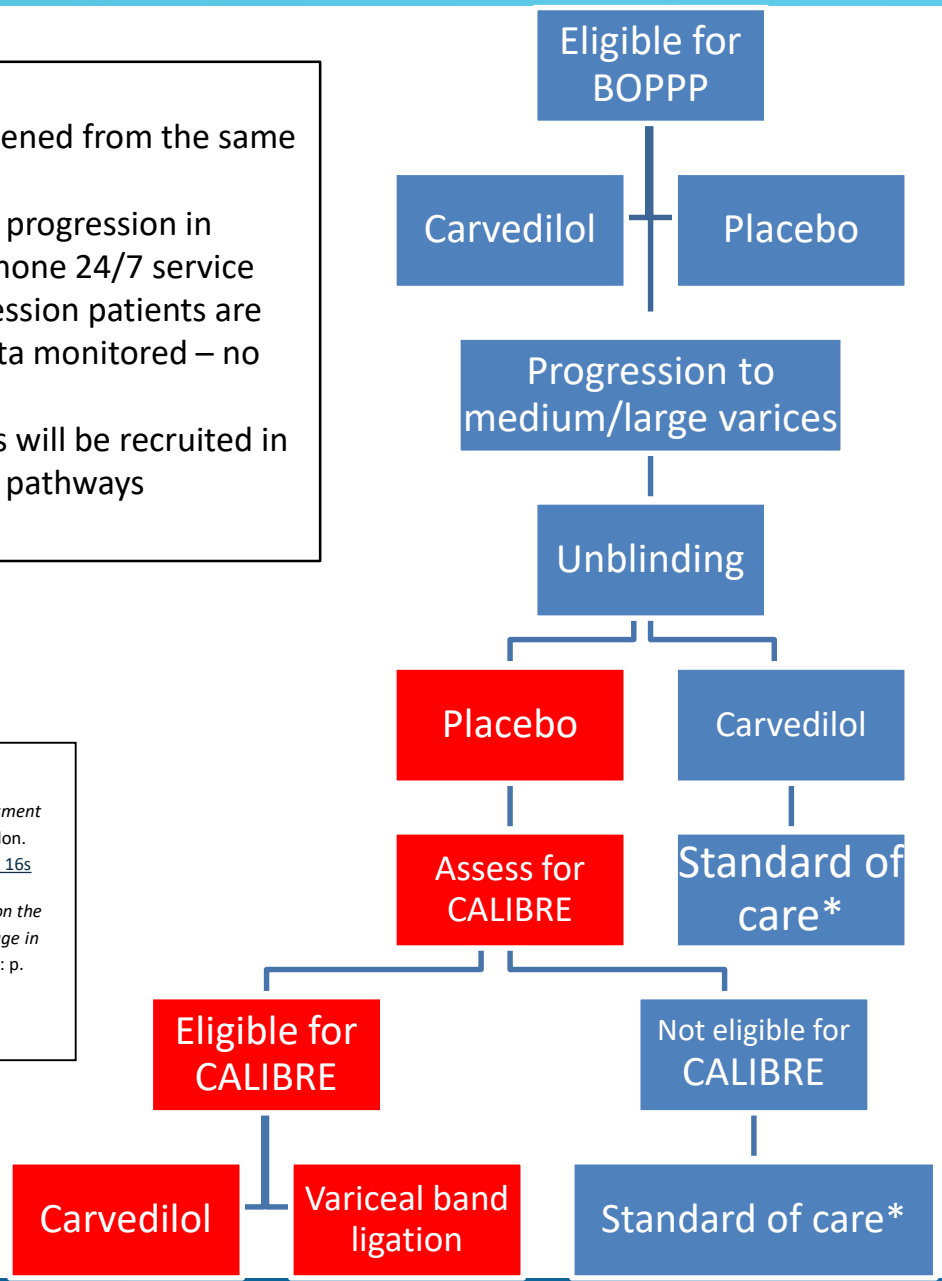




CALIBRE: CALIBRE & BOPPP INTERPLAY

Notes:

- Patients are screened from the same pool
- Unblinding after progression in BOPPP via telephone 24/7 service
- Following progression patients are censored but data monitored – no further CRFs
- CALIBRE patients will be recruited in one of the three pathways



***Standard of care**

1. NICE, *Cirrhosis in over 16s: Assessment and management*. 2016, NICE: London. NICE guideance for Cirrhosis in over 16s

2. Tripathi, D., et al., *UK guidelines on the management of variceal haemorrhage in cirrhotic patients.* Gut, 2015. **64**(11): p. 1680-1704.

CALIBRE: KEY PROTOCOL CHANGES

- Four week carvedilol arm safety visit changed to two week visit.
- Update to exclusion criteria, in particular AAH.
- Update to schemas and the removal of the qualitative study.
- Update to permit remote visits.
- Update to permit written consent to be obtained remotely.
- Further clarification on non-expedited SAE reporting.
- Additional option for withdrawal.

CALIBRE: CONSENT

- Written consent can now be obtained remotely following approval of Protocol v3.0.
- There must be a witness to the consent and the witness must sign and date the ICF.
- The original ICF is to be kept in the Investigator Site File, a copy is to be sent to the participant, a copy to be kept in the patient's records and a copy sent to BCTU.

CALIBRE: INCLUSION CRITERIA

To be eligible to participate in the **CALIBRE** Trial, patients must have **both**:

✓ 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.

and

✓ Medium and/or large varices that have never bled as defined in the BSG guidelines.

CALIBRE: EXCLUSION CRITERIA

- 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 band ligation.
- Presence of malignancy or systemic disease that significantly affects one-year survival.
- Unable to give informed consent.
- Acute alcoholic hepatitis **at the time of randomisation**.
- Patients with surgical or radiological porto-systemic shunts such as transjugular portosystemic stent-shunt (TIPSS).
- Previous organ transplantation.

CALIBRE: BASELINE VISIT

- Clarification of exclusion criteria (AAH)
- *Additional standard care blood tests added - please ensure INR is recorded OR both PTT (Control) AND PTT (Patient)*

NOTE:

- Vital signs, height and weight are important to capture.
- Complete EQ 5D-5L *- please put trial number and date completed on front of the questionnaire*
- Make follow up appointment at 2 weeks (if applicable)

CALIBRE: TWO WEEK VISIT

- Changed to 2 week visit.
- Type of visit added.*

**Please note that a face to face visit is preferred however a remote visit is permitted. If face to face, we expect vital signs to be recorded.*

If a remote consultation results in face to face visit please only complete one CRF for face to face visit.

NOTE:

- Medication review
- Adverse event review and evaluation

CALIBRE: 6 AND 12 MONTH VISIT

- Type of visit added.* If remote visit is ticked on the CRF, certain data will not be expected i.e. vital signs.

  **If a remote consultation results in face to face visit please only complete one CRF for face to face visit.*

- Tested positive for COVID-19 added.
- Fully vaccinated against COVID-19 question added.
- Additional standard care blood tests – *please ensure INR is recorded OR both PTT (Control) AND PTT (Patient)*
- If an alternative treatment has been commenced due to reasons other than AEs added.

NOTE:

- Complete EQ 5D-5L – *please put trial number and date completed on front of the questionnaire*
- Treatment Adherence

- Please ensure all questions have an answer. If the Participant has switched arms, please complete both the Carvedilol and VBL questions.

CALIBRE: CRF CHANGES OVERVIEW

- Randomisation CRF v7.0 – Update to exclusion criteria, in particular AAH.
- Baseline CRF v4.0 – Additional questions regarding COVID status.
- 2 Week FU CRF v3.0 – 4 week visit amended to 2 week and type of visit added.
- 6 and 12 Month CRF v4.0 – Type of visit added, additional questions regarding COVID status, alternative treatment due reasons other than AEs added.
- Change of Status CRF v3.0 – Qualitative withdrawal has been removed, allow withdrawal at the request of the CALIBRE Trials Office added.
- SAE Form v3.0 – Amended to collect partial Date of Birth only.

CALIBRE: OTHER DOCUMENT CHANGES

- PIS v4.0 – Further clarification added following the findings from the qualitative research study.
- ICF v4.0 – Witness details added for written consent obtained remotely.
- GP Letter v2.0 – Amended 4 week visit to 2 week.

CALIBRE: SAE REPORTING

The below is a list of SAEs that are expected in this cohort of patients and therefore DO NOT require expedited reporting on a SAE form and are instead recorded on the 6 and 12 month CRFs:

- Variceal bleeding
- Banding-related bleeding
- Hepatic encephalopathy
- Ascites
- Hepatocellular carcinoma
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome

** If you are in any doubt, please contact the CALIBRE trials team.*

CALIBRE: RESTART FOLLOWING PAUSE

- Recruitment can resume once your site has received the greenlight following confirmation of:
- Recommencement of variceal surveillance
- PI oversight
- Research staff are in place to support the trial
- Confirmation of capability and capacity from your R&D department

SITE FAQS

Q: Acute alcoholic hepatitis is an exclusion criterion, is there a category on this exclusion i.e. if they are mild, could they be included or does it not matter and sites exclude all regardless of severity?	• A: We have clarified this in the updated Protocol V3.0. Providing the participant does not have AAH at the point of randomisation, they can be included.
Q: If patients are on non-selective beta blockers i.e. carvedilol, propanol, nadolol for short term i.e. less than 7 days and now have stopped taking the medication could they be included?	• A: No. Any previous use of non-selective beta blockers are an exclusion.
Q: If a patient is on a selective beta blocker for heart issues for instance, could they be included?	• A: Cardiology will need to be consulted. Dose equivalence is important with selective beta-blockers. In CALIBRE the top dose of carvedilol is 12.5mg/24h, and this may not be sufficient for rate control or blood pressure control when switching from a selective beta-blocker. For further clarification, please contact the trials team.
Q: If a patient has had a previous liver resection for HCC, would that make them ineligible for CALIBRE?	• A: As long as the patient has clear evidence of cirrhosis in the background liver and the 1 year survival is not affected by the disease (assuming to be curative) then they can be included.

CRN RESEARCH NURSE SUPPORT

CALIBRE TRIAL MANAGEMENT GROUP

Clinical

Prof 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 of Research and Development)

Dr Margaret Grant (Director of Operations)

Dr Jonathan Mathers, Mr Christopher Poyner (Qualitative research)

Prof Susan Jowett (Professor of Health Economics)

Dr Kelly Handley (Senior Medical Statistician)

Gemma Slinn (Trials Management Team leader)

Lisa Holden (Trial Manager)

Email: calibretrial@trial.bham.ac.uk

Twitter: @CalibreTrial

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

NIHR | National Institute for Health Research

MANY THANKS TO COLLABORATORS

and the participants

QUESTIONS??

Thank you for listening.

Please remember to add this training to your Training Log and send to the CALIBRE Trials Office.

Are there any questions?

NEXT REFRESHER TRAINING

The next Refresher Training Webinar

will be held on

Wednesday 8th December 2021 at 1pm.