CALIBRE TRIAL COLLABORATORS

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

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CALIBRE: STUDY DESIGN

Randomised controlled parallel group trial

Open-label

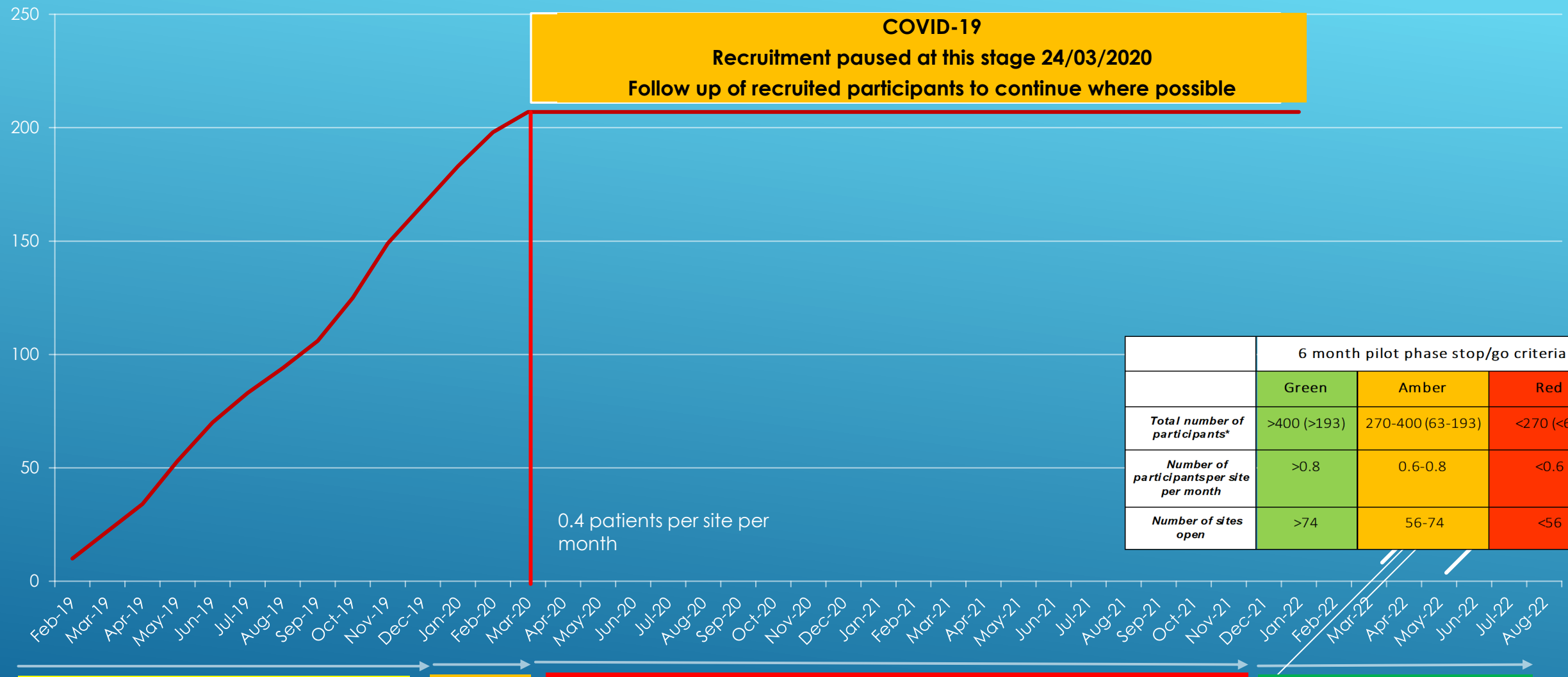
Two interventions:

Carvedilol vs. Variceal Band Ligation

2630 participants

12 month follow-up

CALIBRE: PILOT



	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

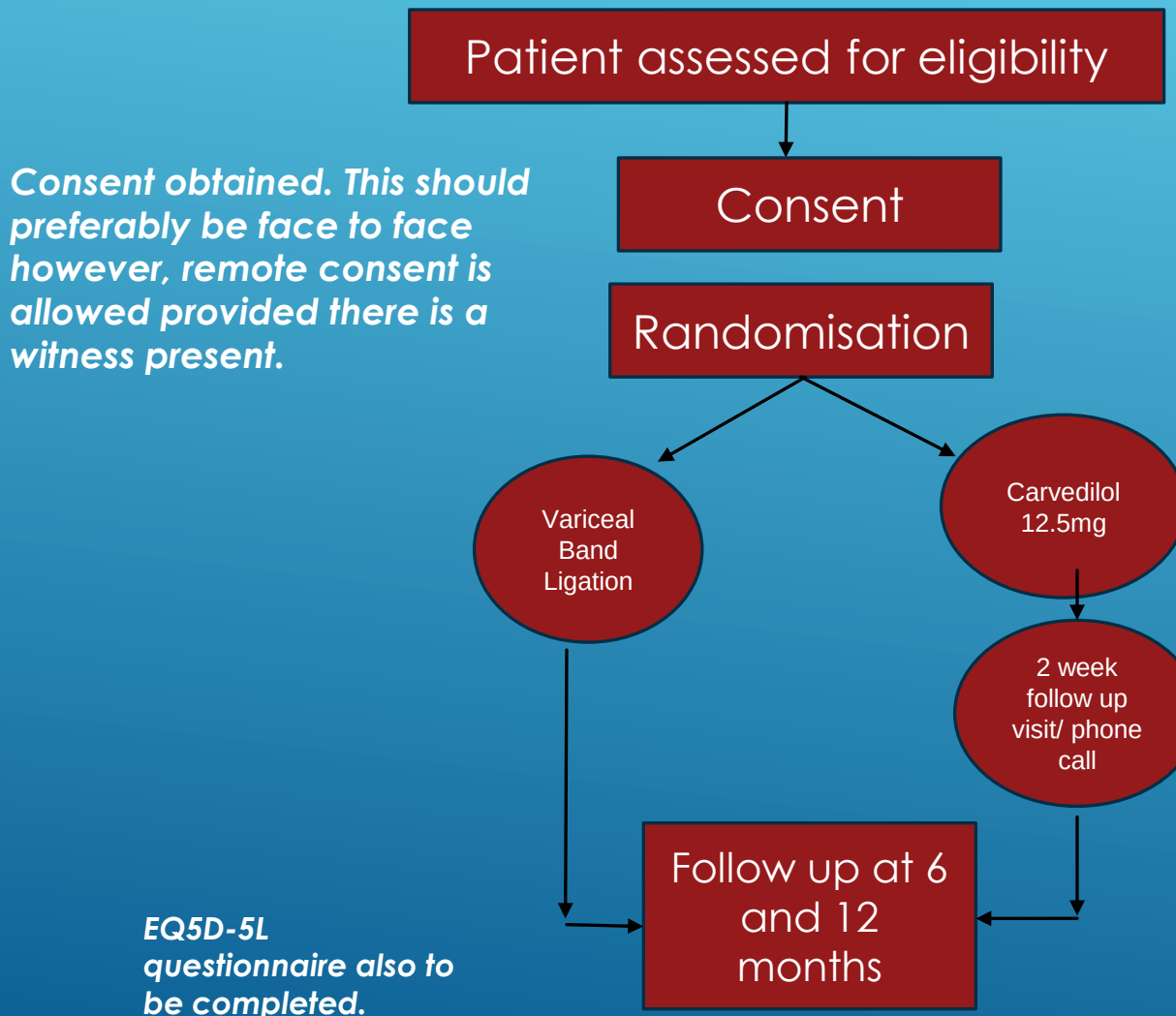
- **To remain paused in light of COVID-19 and impact on endoscopy services.**
- **HTA monitoring meeting – November 2020**
- **Advise to continue to suspend for 6/12**
- **Recovery plan - HTA Monitoring meeting – July 2021**
- **Green light to start process of resuming recruitment September 2021**

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 research delivery managers (RDM). • 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

Figure 1: Consent process (planned endoscopy where no diagnosis of varices has yet been made

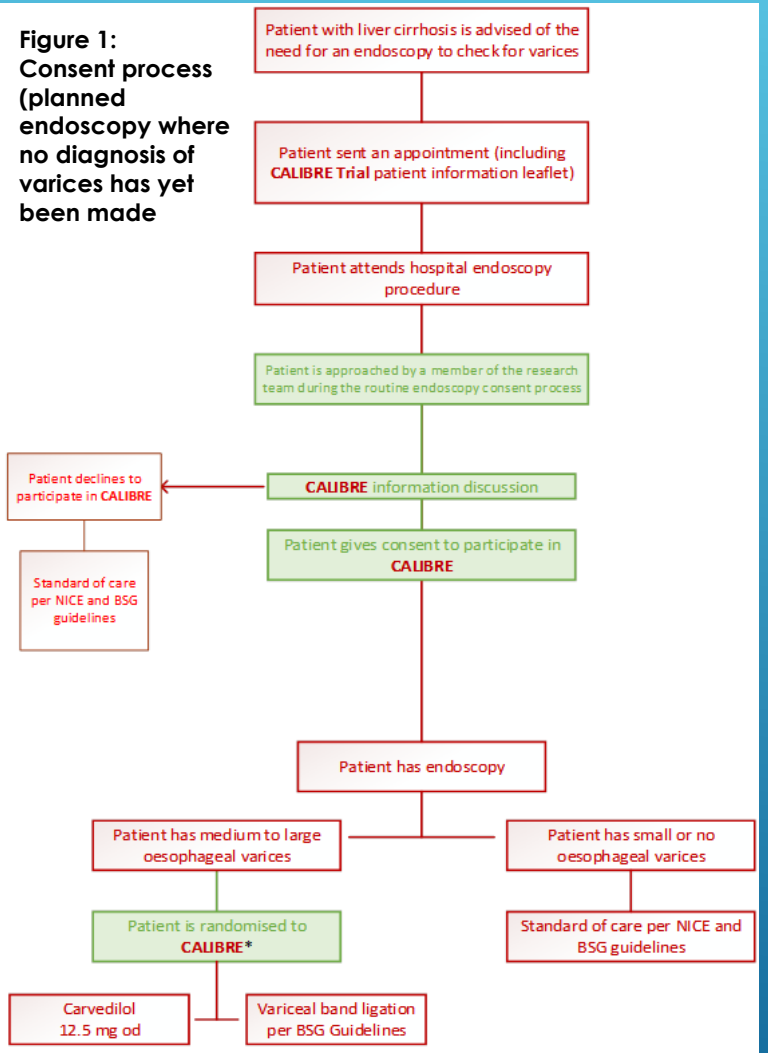


Figure 2: Consent process following referral from an outpatient clinic following diagnostic endoscopy

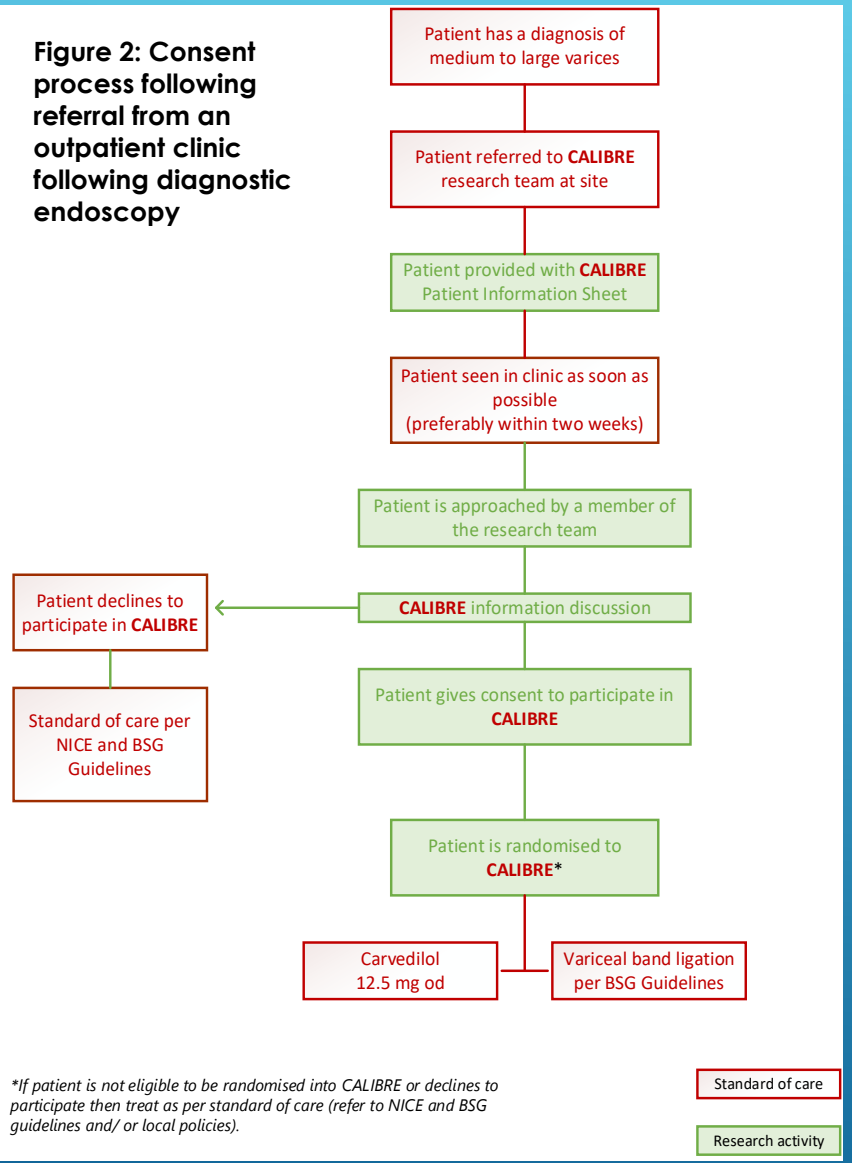
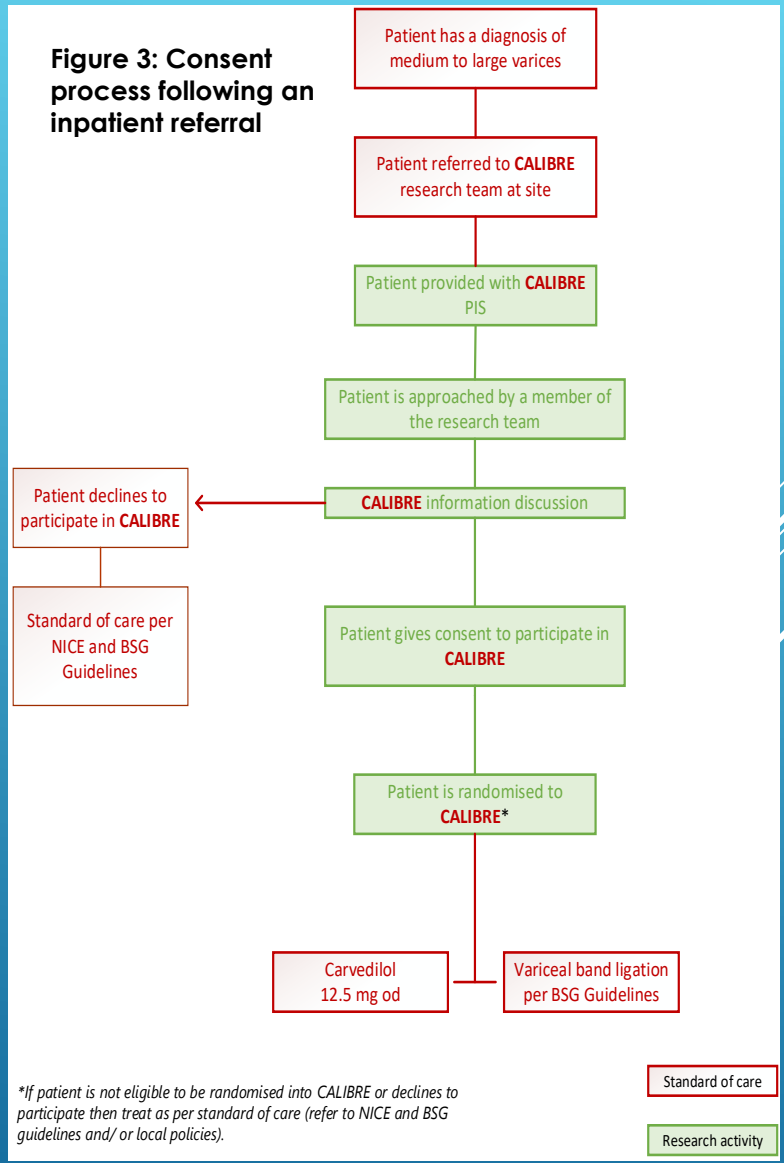


Figure 3: Consent process following an inpatient referral



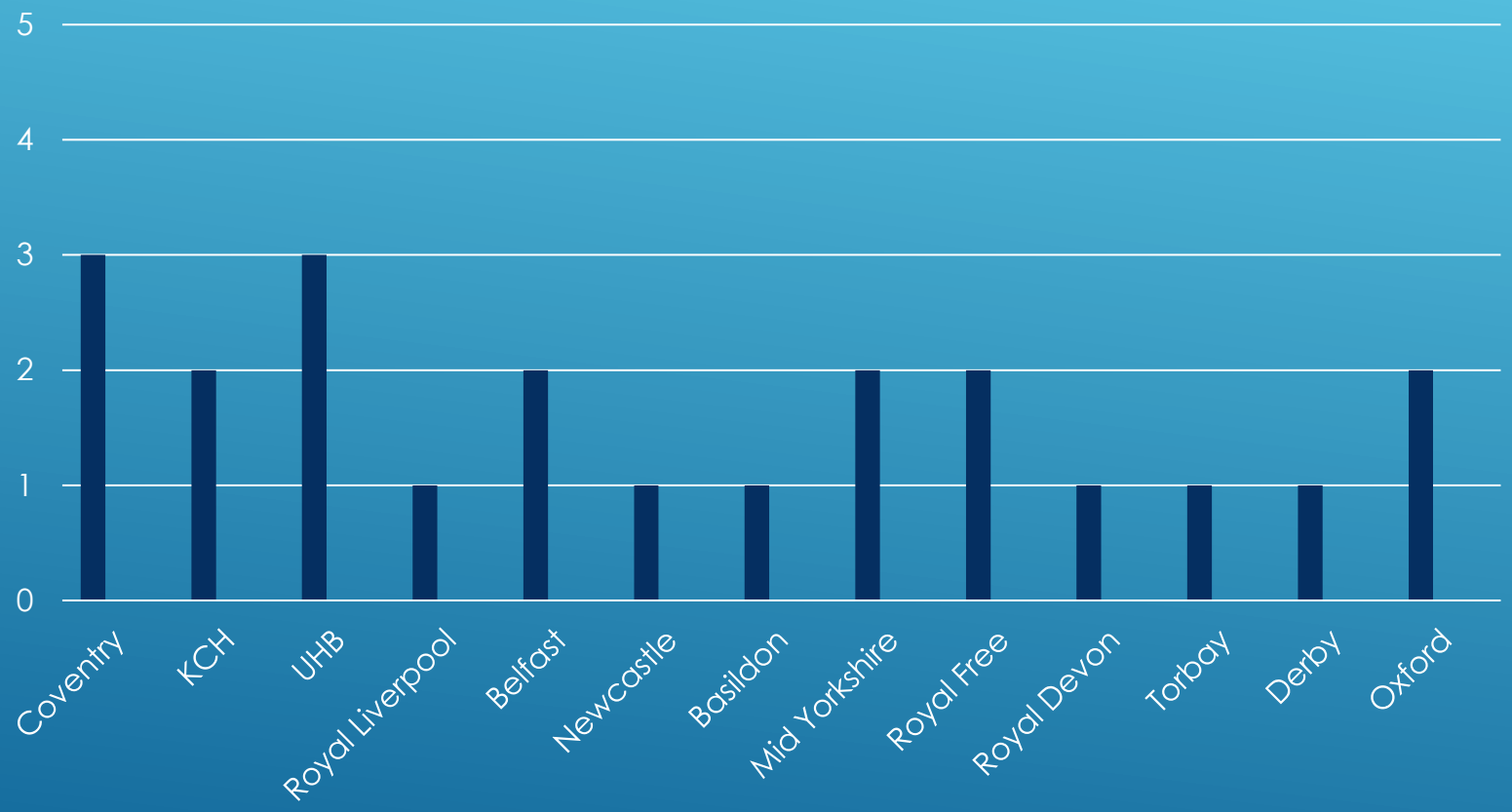
CALIBRE: SITES OPEN

Aberdeen	Aintree	Basildon	Basingstoke
Belfast	Coventry	Cambridge	Cardiff
Derby	Dundee	Edinburgh	Gateshead
King's College	Leicester	Durham	Mid Yorkshire
Glasgow Royal Infirmary	Guy's & St Thomas	Hull	Newcastle
North Tyneside	Plymouth	Portsmouth	Oxford
Royal Devon	Royal Glamorgan	Royal Liverpool	Scarborough
Sheffield	Shrewsbury	South Tees	Southampton
Swindon	South Tyneside	Imperial College	Chelsea & Westminster
St George's	Sunderland	Torbay & South Devon	Bedford
York	Walsall	Wolverhampton	UHB
Nottingham	Royal Free	Royal London	Dudley
Wigan	Bournemouth	Sandwell	

CALIBRE: SITES DUE TO OPEN SOON

Luton & Dunstable	Homerton	Bradford
Norfolk & Norwich	Swansea	Royal Cornwall
Bristol Royal Infirmary	Kettering General	Leeds

CALIBRE: RECRUITMENT FOLLOWING PAUSE



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- **207 participants at start of pilot**
- **22 participants recruited so far from 51 sites (229 cumulative total)**
- **Target is a minimum of 270 participants by 5th July 2022**
- **Minimum of 41 participants need by 5th July 2022**
- **Easily achievable if each of site recruited 1-2 participants by 5th July 2022**

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.

SITE FAQS

Q: Does the witness on the Informed Consent Form need to be on the Delegation Log?	• A: We have not mandated who the witness is providing they witnessed the discussion with the patient.
Q: Do CRFs need to be posted to BCTU or can they be emailed?	• A: They can be sent by email if it is secure and encrypted, otherwise they would need to be posted. Please ensure ICF and Randomisation Form are sent separately as they have identifiable information.
Q: What if the PI is not available to sign the SAE?	• A: A SAE with minimal information can be emailed to BCTU within 24 hours of site being made aware of the event. Causality assessment can be carried out by a medically qualified person delegated the duty to complete SAEs on the Delegation Log.
Q: What happens if the GP won't prescribe carvedilol?	• A: If the GP is not happy to prescribe then secondary care should prescribe for the duration of follow up i.e. one year from randomisation and the GP should be advised to continue thereafter. Carvedilol is standard of care medication taken from NHS stocks, so GPs should provide repeat prescriptions as patients would need treatment on an indefinite basis regardless of the trial.

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)

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Dr Kelly Handley (Senior Medical Statistician)

Gemma Slinn (Trials Management Team leader)

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: Contact Lisa Holden to join What's App group

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QUESTIONS??

Thank you for listening.

Are there any questions?