Site Initiation Visit



Lisa Holden Trial Manager







<u>Carvedilol</u> versus variceal <u>band</u> ligation in primary prevention of variceal bleeding in liver cirrhosis

Protocol Version: 3.0, 7th September 2021



Team Leader: Gemma Slinn

CI: Prof. Dhiraj Tripathi

Sponsor: University of Birmingham

Funder: National Institute for

Health Research (NIHR)

(Reference 16/99/02)

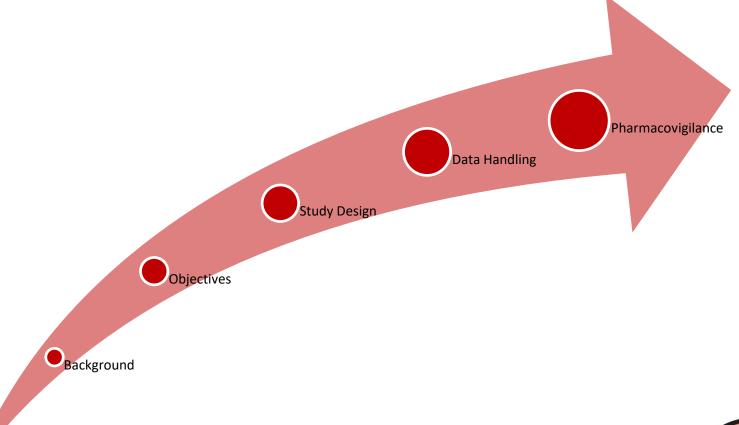








Agenda

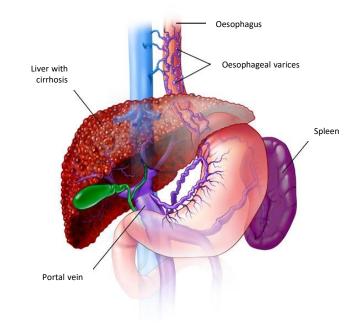




Background: Liver Cirrhosis

5th largest cause of death in the UK

Average age of death is 59 years



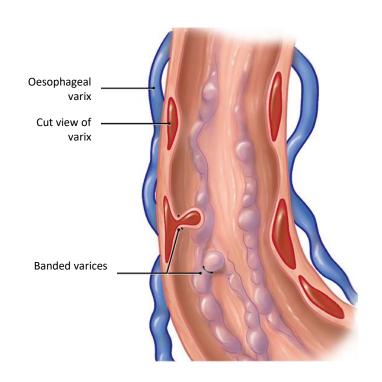
Causes a great economic impact, due to need for hospitalisation and workforce implications



Background: Variceal Bleeding

A major complication of liver Cirrhosis is variceal bleeding

Variceal bleeding has a 1 year mortality of up to 40%



Aiming to reduce the risk of the first variceal bleed



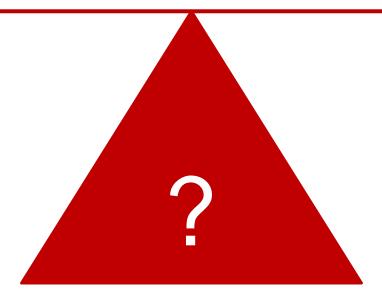
Trial Rationale

There is disparity in current UK guidelines with regards to primary prevention of variceal bleeding in patients with medium to large varices.

NICE 2016¹: Use VBL as first line

BSG 2015²:

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



National Institute for Health and Care Excellence



² The British Society of Gastroenterology

Trial Rationale cont.

Current evidence comparing the two treatments is based on underpowered and low quality trials

A large randomised controlled trial would help clinicians decide on the best treatment



Primary Objective

To compare carvedilol versus variceal band ligation in preventing any variceal bleeding within 1 year of randomisation in patients with cirrhosis and medium to large oesophageal varices that have never bled



Secondary Objectives

To investigate the effect of carvedilol and variceal band ligation on survival, development of other complications of cirrhosis and adverse events

To assess cost-effectiveness, patient preference and use of alternative or cross-over therapies



Study Design

Randomised controlled parallel group trial

Open-label

Two interventions:

Carvedilol vs. Variceal Band Ligation

75 sites

2630 participants

12 month follow-up



Internal Pilot Trial (Jan 22 – Jul 22)

Must meet the following targets to justify progression:

>400 participants

>74 sites

1 patient per month per open site

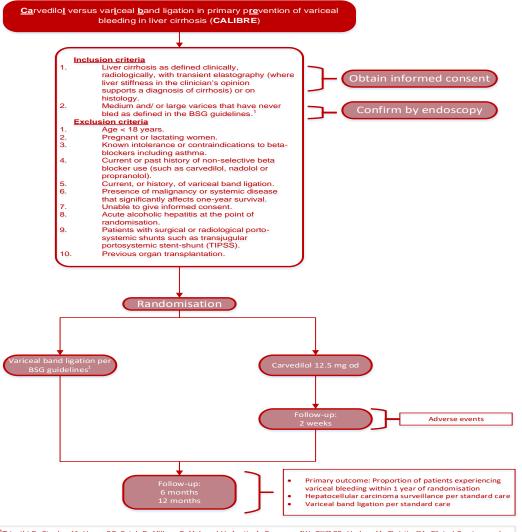
3 new sites per month

90% of patients complete data collection at their 6 month follow-up visit

No safety concerns which would prohibit continuation



Trial Summary



¹Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, Austin A, Ferguson JW, Olliff SP, Hudson M, Christie JM; Clinical Services and Standards Committee of the British Society of Gastroenterology. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut. 2015 Nov;64(11):1680-704.



Eligibility – Inclusion

Inclusion Criteria

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



Eligibility – Exclusion

Exclusion Criteria

Age less than 18 years

Pregnant or lactating women

Known intolerance or contraindications to beta-blockers including asthma

Unable to give informed consent

Acute alcoholic hepatitis at the point of randomisation.

Current or past history of non-selective beta blocker use (such as carvedilol, nadolol or propranolol)

Current, or history, of Variceal band ligation

previous organ transplantation

Presence of malignancy or systemic disease that significantly affects 1 year survival

Patients with surgical or radiological portsystemic shunts such as tranjugular portosystemic stent-shunts (TIPSS)



Recruitment

A medically qualified doctor who is delegated the duty on the Delegation Log must confirm participant eligibility

Participants may be identified and recruited by:

Planned endoscopy

Outpatient clinic referral

Inpatient referral

Only participants who have not yet started treatment will be eligible



Figure 1: Protocol V.3.0 page 32

Consent process (planned endoscopy where no diagnosis of varices has yet been made)

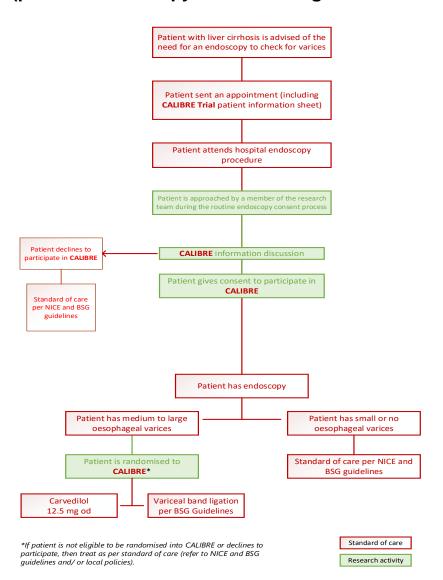
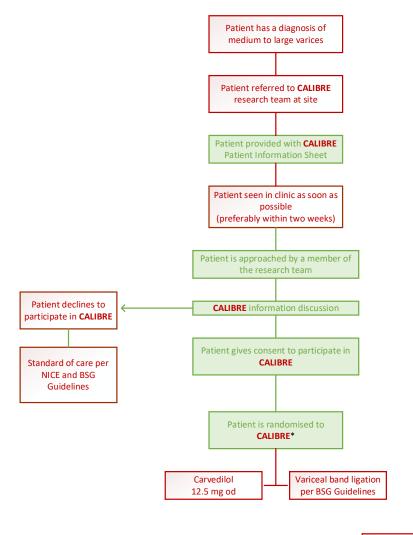




Figure 2: Protocol V.3.0 page 33

Consent process following referral from an outpatient clinic following diagnostic endoscopy



*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).

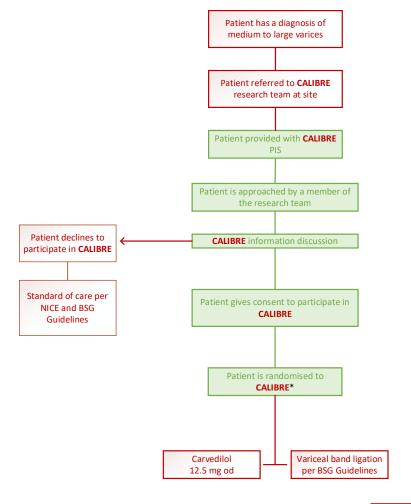
Standard of care

Research activity



Figure 3: Protocol V.3.0 page 34

Figure 3: Consent process following an inpatient referral



*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 quidelines and/ or local policies).

Standard of care

Research activity



Informed Consent

The latest version of the Informed Consent Form must be completed by the participant if consent is obtained face to face or completed by research staff and witnessed if written consent is obtained remotely.

A copy of the ICF must be:

Given/sent to the patient

Sent to BCTU

Filed in the participant's medical notes

The original ICF must be placed in the Investigator Site File



TO BE PRINTED ON LOCAL TRUST HEADED PAPER

Example ICF

Informed Consent Form

<u>Carvedilol</u> versus var<u>i</u>ceal <u>b</u>and ligation in primary <u>pre</u>vention of variceal bleeding

in liver cirrhosis - CALIBRE Neil Rajoriya University Hospital Birmingham Principal Investigator:.... Site name: Participant Trial Number: Please initial each box to confirm consent I confirm that I have read and understood the information sheet, version number 4.0 for the CALIBRE Study. I have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that data collected up to my time of withdrawal may be used. I understand that relevant sections of my medical notes and information collected during the study may be looked at by individuals from the CALIBRE Study Research Team, representatives of the LH sponsor, from regulatory authorities, or from the NHS Trust/ Health Board, where this is relevant to my taking part in this research. I give permission for these individuals to have direct access to I agree to my GP being informed of my participation in this study and that they may be contacted by members of the research team for follow-up information. Information collected that identifies me by name, e.g. consent forms as well as contact address LH and email, will be transferred from where it is collected and stored at the University of Birmingham during the trial and at a specialist archiving facility, in compliance with current regulations, after the trial. I agree to the transfer and storage of this information. To permit the accurate follow-up of all participants it may be necessary for the CALIBRE Study LH Research Team to contact other UK NHS bodies to provide information about your health status. I hereby give consent for the use of information held and maintained by e.g. the Health and Social Care Information Centre and other central UK NHS bodies to contact participants or provide information about their health status by using my NHS number/ Community Health Index (CHI) or Health & Care number (H&C). LH I agree to take part in the CALIBRE Study.

Name of participant: Date: Signature: Lisa Holden Lisa Holden 5th January 2022 Name of person taking consent: Date: Signature: Dhiraj Tripathi Dhiraj Tripathi 5th January 2022 Name of witness: Signature: Date: 5th January 2022 Kate Brailsford Kate Brailsford

To continue participating in the CALIBRE Study you <u>MUST</u> consent to points 1-7 above and initial the corresponding boxes.

A witness is mandatory for remote consent.

Original to be filed in the Investigator's Site File; 1 copy for participant; 1 copy to be kept with patient's hospital record; 1 copy to be sent to BCTU



Randomisation

Randomisation will be provided by a secure online randomisation system at BCTU.

Unique usernames and passwords provided

Available 24 hours a day, seven days a week

The CALIBRE Trials team are available Monday to Friday 09:00 to 17:00 UK time, except for bank holidays and UoB closed days



Randomisation cont.

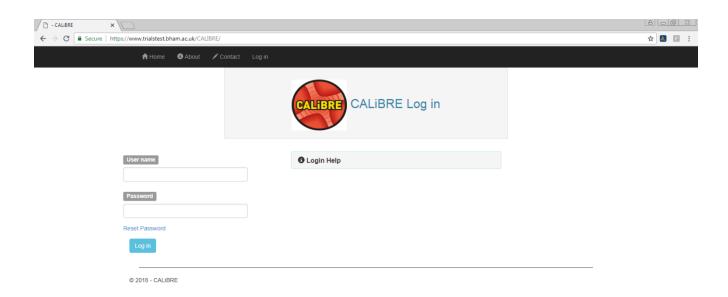
Randomisation may begin after participant eligibility has been confirmed and informed consent has been received

A Randomisation Form must be completed before a trial number can be obtained

If data items are missing, randomisation will be suspended, but can be restarted once the information is available

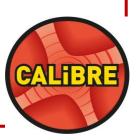


Randomisation Form Example



https://www.trials.bham.ac.uk/CALIBRE

https://www.trialstest.bham.ac.uk/calibre for training prior to going on live randomising (Use for training purposes only) (Logon: BCTU-ITHelp@adf.bham.ac.uk Password: Bctutester2)



Treatments

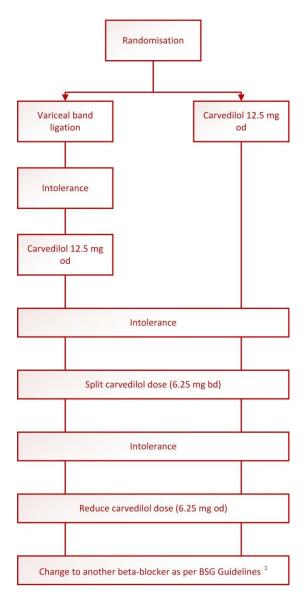
Carvedilol:

Participants will be prescribed 12.5mg od for the 12 months that they are in the trial. They will be seen in a follow up clinic at two weeks to assess for any short term adverse events.

Variceal Band Ligation:

Varices are banded at regular intervals (usually 2-4 weekly) until they are eradicated. After successful eradication of varices, further endoscopies should be carried out as per local standard practice. Any recurrent varices (i.e. medium to large varices) are treated with further variceal band ligation usually at 2-4 weekly intervals until eradication and then offered repeat endoscopies as per local standard practice.

Treatment Modification





Schedule of Assessments

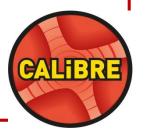
	Randomisation and Baseline	2 weeks ^v ± 1 week FU visit	6 months ± 2 months FU visit	12 months ± 2 months FU visit
Confirm eligibility	✓			
Seek informed consent	✓			
Randomisation	✓			
Medical history#	✓			
Medication review	✓	✓	✓	✓
Physical examination	√ *		√ *	√ *
Office blood pressure	✓	✓	✓	✓
Pulse	✓	✓	✓	✓
Standard care blood tests	√ *		√ *	√ *
Height	√ *			
Weight	√ *	√ *	√ *	√ *
Administer EQ 5D-5L	✓		✓	✓
Resource use (Follow-Up CRFs)			✓	✓
Dispense trial medication ^{¥ ∞}	✓			
Adverse event review and evaluation		1	✓	1
Adherence			✓	✓

#Including aetiology of liver disease and past medical history (diabetes, ischaemic heart disease, pulmonary disease).

*Taken from clinical records.

[¥]Carvedilol arm only.

∞Medication may initially be dispensed by site but can subsequently be dispensed by the participant's community pharmacy.



Primary Outcome

Any variceal bleeding within 1 year of randomisation



Secondary Outcomes

Time to first variceal bleed (in days) from randomisation

Mortality at 1 year from randomisation:

All-cause mortality

Liver-related mortality

Cardiovascular mortality

Transplant free survival at 1 year from randomisation



Secondary Outcomes cont.

Adverse events related to treatment (up to 12 months after randomisation)

Other complications of cirrhosis

Patient preference

Health-related quality of life (EQ-5D-5L) at trial entry, 6 months, and 12 months



Secondary Outcomes cont.

Use of alternative therapies

Crossover therapies



Patient Withdrawal

Participant withdrawn from the trial intervention, but will be followed up in accordance with the schedule of assessments (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).

Participant withdrawn from the trial intervention and will no longer attend trial visits in accordance with the schedule of assessments (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).



Patient Withdrawal cont.

Participant withdrawn from trial intervention and will no longer be followed up for the purposes of the trial and no further data will be collected i.e. only data collected prior to the withdrawal can be used in the trial analysis).

Participant withdrawn at the request of the **CALIBRE** Trial Office because of significant non-compliance with the **CALIBRE** trial protocol. The participant will not to be followed up for the purposes of the trial and no further data will be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis).



DATA HANDLING









Source Data

Patient Reported Data (EQ-5D-5L)

Laboratory Results

Clinical Event Data

Health Economics Data

Withdrawal (if applicable)

Recruitment



Case Report Forms

CRFs will be paper records completed on site

CRFs are considered complete when all data fields are completed unambiguously or the data is marked as unobtainable

The original or copy of each completed CRF should be sent to BCTU, and a true copy filed in the ISF



Case Report Forms - Baseline

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Trial number:	CONFIDENTIAL WHEN COMPLETE
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Does the participant drink coffee daily? No Yes	If no, please continue to Ascites. If yes, please complete the following question.
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Spontaneous Bacterial Peritonitis	
Has the participant ever been diagnosed with bacterial	
peritonitis?	If yes, please complete the following question.

Trial number:	-	CONFIDENTIAL WHEN COMPLETE
CONCOMITANT MEDICATIONS		
Is the participant taking any of the	following medications curr	ently?
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Potassium-sparing diuretics	ш	
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Antibiatics (#> 1 month)		
Antiviral agent		
Ursodeoxycholic acid		
Obeticholic Acid		
Fibrate		
Other (please specify)		
I confirm that all above items hav	e been considered and only	y those ticked are being taken No Yes

CALIBRE BASELINE CRF		v4.0, 8 ⁶ November 2021
EudraCT No.: 2018-002488-24		
	Page 4 of 12	

Trial number	et	C	ONFIDENTIAL WHEN COMPLETE
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Version Control CRFs

Document Name	Version Number	Version Date
Randomisation Form	7.0	08/11/2021
Baseline CRF	4.0	08/11/2021
2 Week Follow-Up CRF	3.0	08/11/2021
6 Month Follow-Up CRF	4.0	08/11/2021
12 Month Follow-Up CRF	4.0	08/11/2021
Pregnancy Notification	2.0	08/04/2019
Serious Adverse Event Form	3.0	08/11/2021
Change of Status Form	3.0	08/11/2021



Data Management

Missing and ambiguous data will be queried using a data clarification system

Staff from BCTU will transcribe data from paper CRFs to an online database

Site staff will not have access to alter the CRF online database but will be given a read-only view



Data Security

Physical Security Measures

Access Control

Network Security Measures

System Design and Management

Operational Processes

Data Processing

Data Protection Registration

System Audit



PHARMACOVIGILANCE









Definition: Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment



Definition: Adverse Reaction

Any untoward and unintended response in a subject to an investigational medicinal product which is related (or for which a causal relationship cannot be ruled out) to any dose administered to that subject



Definition: Unexpected

An adverse reaction, the nature and severity of which is not consistent with the information in question set out in the SmPC¹ or the IB² for that product



Summary of Product Characteristics

² Investigator's Brochure

Definition: Serious

Any adverse event, adverse reaction, or unexpected adverse reaction that:

Results in death

Is life-threatening

Requires hospitalisation or prolongation of existing hospitalisation

Results in persistent or significant disability or incapacity

Consists of a congenital abnormality or birth defect



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. Instead these events are recorded on the 6 and 12 month follow up CRFs:

Variceal Bleeding

Banding-related bleeding

Hepatic Encephalopathy

Ascites

Hepatocellular carcinoma

Spontaneous bacterial peritonitis

Hepatorenal syndrome



Reporting

All adverse events must be recorded in the medical records, and reported to BCTU

AEs and **Expected** SAEs: Recorded on follow-up CRFs at 6 months and 12 months

Non Expected SAEs:

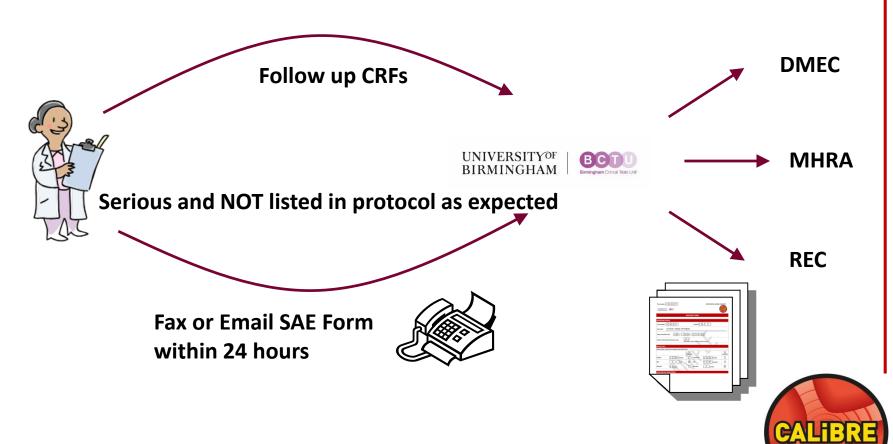
Recorded on specific form and securely emailed or faxed to BCTU within 24 hours

BCTU will report to DMEC, MHRA and REC as appropriate



Reporting

Serious but listed on page 46 of the protocol as expected



Example SAE Form



SAE Ref::/			CONFIDENTIAL WHEN COMPLETE
TRIAL TREATMENT			
Where drug interventions (RMP) have been	n stopped		
Did the event abate on stopping drug?	No	Yes	Not applicable
If yes please provide details:			
Did the event reappear after introduction of drug?	No	Yes	Not applicable
Fyes please provide details:			

SERIOUSNESS OF E					
	ness of event rsponse to each question)	No	Yes	Date of death:	Details DD / MMM / YYYY
		٦	Γ	Cause of death:	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
Life threatening ex-	ent:		L		
In-patient hospitalise existing hospitalise	sation or prolongation of tion:	٦	Г	Prolonged Date of discharge:	DD / MMM / YYYY
Persistent or signific Congenital anomaly	cant disability/incapacity: y or birth defect:	=	F		,,
Other medical reas	on for reporting?	_	L	Please specify:	
Date of Onset:	DD/MMM/YYY	7	Date 8	ecame Serious:	DD/MMM/YYYY
Date Site Became Aware:	DD/MMM/YYY			esolved:	DD/MMM/YYYY

Drug Name	Route 1-Onl 2-W	1-Chul (including units and			Yes oing?	If yes, please complete below Stop Date (if relevant)
	B-Subcutaneous 4-Other (specify)			No	Yes	
			DD / MMM / YYYY	L		DD/MMM/YYY
			DD/MMM/YYYY	L		DD/MMM/YYY
			DD/MMM/YYYY	L		DD/MMM/YYY
			DD / MMM / YYYY	L	\Box	DD/MMM/YYY
			DD/MMM/YYYY	L		DD/MMM/YYY
			DD/MMM/YYYY	L	\Box	DD/MMM/YYY
			DD/MMM/YYYY	L	\Box	DD/MMM/YYY
			DD/MMM/YYYY	L		DD/MMM/YYY
			DD/MMM/YYYY	L		DD/MMM/YYY
			DD/MMM/YYYY	L	\Box	DD/MMM/YYY
			DD/MMM/YYYY	L		DD/MMM/YYY
			DD/MMM/YYYY	L		DD/MMM/YYY

Intervention	Interventilen Received (Last dote of lost dose)	Route	Dose	Intervention Start Date	Action Taken 1-None 2-Intervention Suppord 3-Intervention Delayed 4-Intervention Bedurnd	Intervention Stopped Date	Causality Assessment 1-threlated 7-thilkely to be related 3-Possibly related 4-Probably cristed N-thelistely related
Carvedilol	DD/MMM/YYYY	Oral		DD/MMM/YYYY		DD/MMM/YYYY	
Variceal band ligation	DD/MMM/YYYY	N/A	N/A	DD/MMM/YYYY		DD/MMM/YYYY	
(This must be u	sment undertaken by: ndertaken by a medically qualif lelegated the task)	led doctor					

SAE Ref.:/		CONFIDENTIAL	WHEN COMPLETE
RELEVANT MEDICAL HISTORY (pro-	vide narrative if relevant to diagno	sis)	
Hease provide a narrative if releva ire relevant (where investigations number only).			
f the event is unrelated, please provide details of an alternative			
f the event is unrelated, please rovide details of an alternative explanation for the event:			
INRELATED EVENT If the event is unrelated, please rooked details of an alternative explanation for the event: DETAILS OF PERSON REPORTING fame of person reporting:	Job title of person reporting:		Date reported:
f the event is unrelated, please rowide details of an alternative explanation for the event:			
If the event is unrelated, please rowide details of an alternative explanation for the event: DETAILS OF PERSON REPORTING fame of person reporting:		Date of signature:	Date reported: DD / MMM / YYYY DD / MMM / YYYY



Urgent Reports

All expedited SAEs and SUSARs **must** be reported to BCTU **within 24 hours** of the site being made aware of the event





P.I. Responsibilities

Each Principal Investigator must:

Read the approved protocol and sign and return the PI page on page 9

Adhere to the approved protocol

Be responsible for enrolling only those patients who meet the eligibility criteria

CALIBRE is registered with the Associate PI Scheme



Investigator Site Files

ISFs should always be kept up-to-date

The ISF will be monitored by study staff or a representative of the sponsor

Keep the following documents in the ISF:

Consent Forms

Paper CRFs

SAE Forms

File Notes



Contact Details

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QUESTIONS







