Site Initiation Visit

Lisa Holden
Trial Manager

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

NIHR | National Institute for Health Research

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

Protocol Version: 3.0, 7th September2021

Team Leader:	Gemma Slinn
CI:	Prof. Dhiraj Tripathi
Sponsor:	University of Birmingham
Funder:	National Institute for Health Research (NIHR) (Reference 16/99/02)

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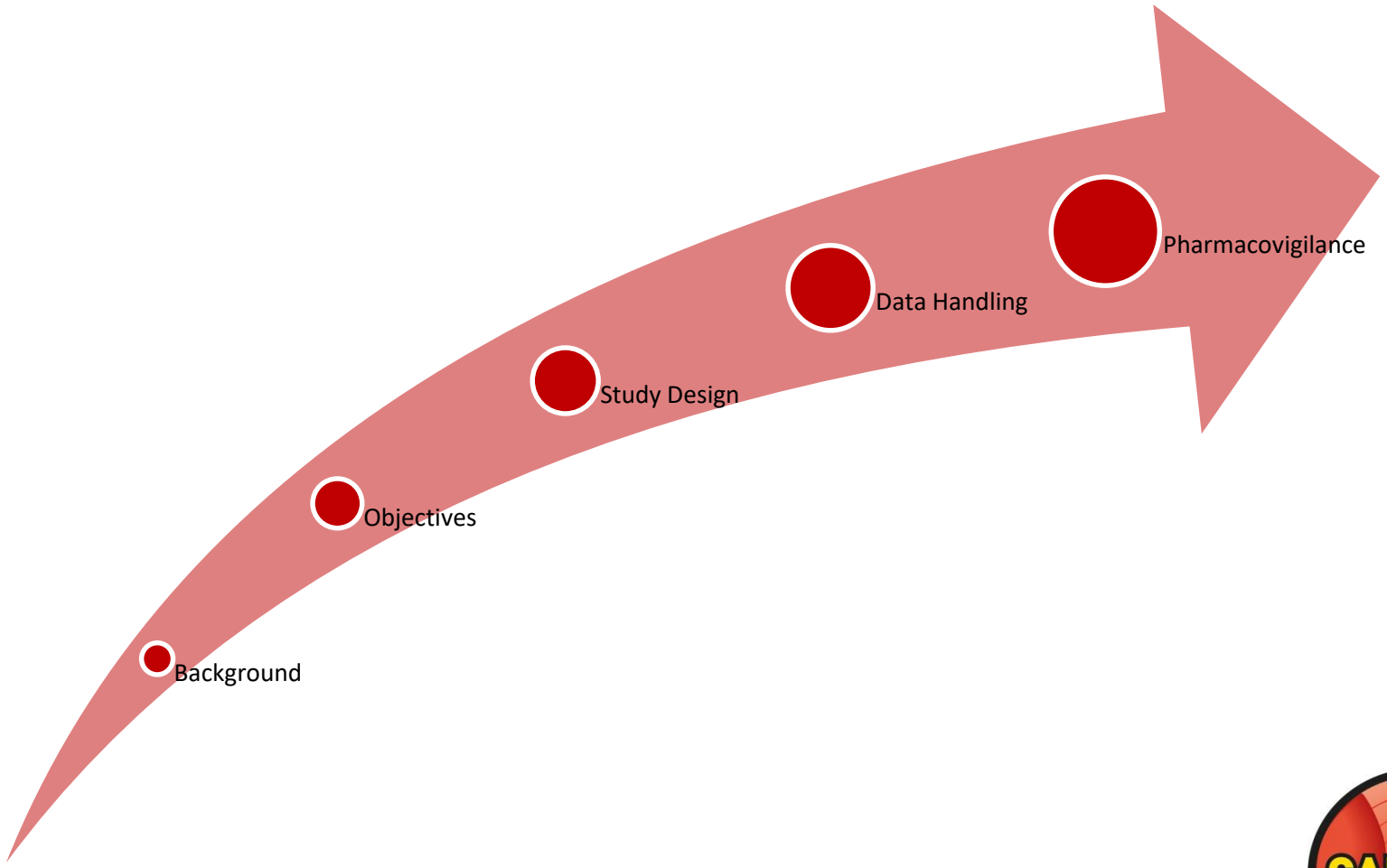
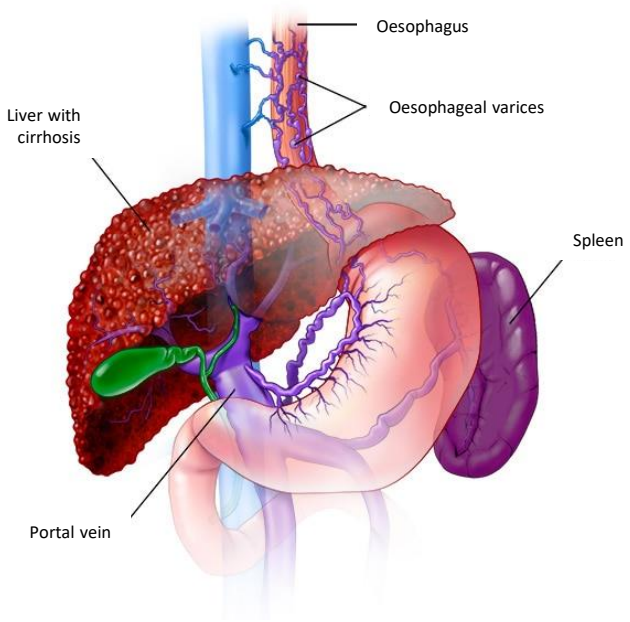
Agenda


Pharmacovigilance
Data Handling
Study Design
Objectives
Background

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

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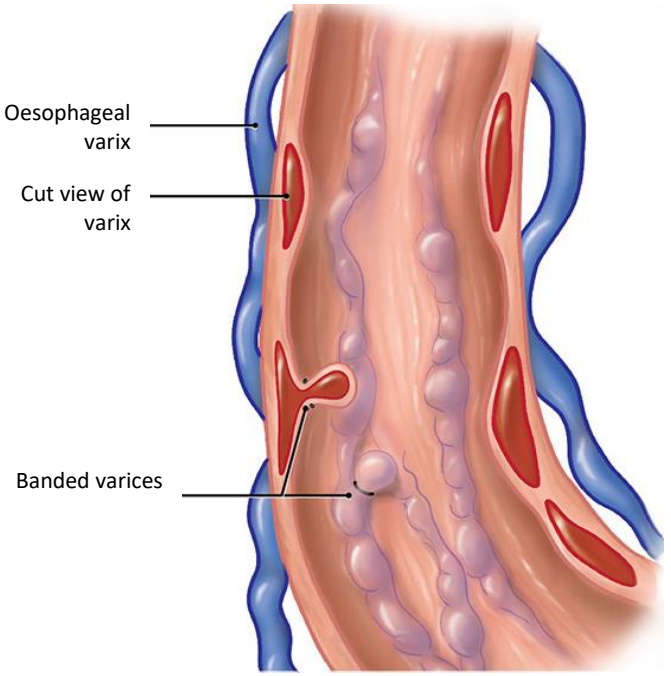
Background: Variceal Bleeding

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

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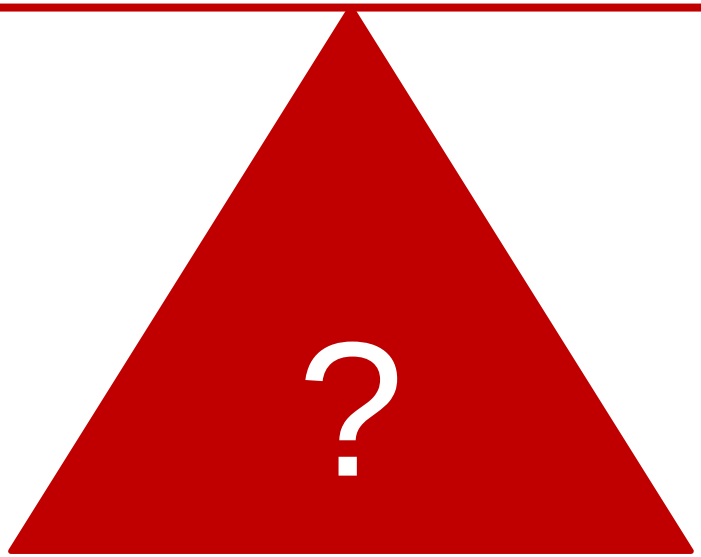
Trial Rationale

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

NICE 2016[1]:
Use VBL as first line

BSG 2015[2]:
Recommends VBL or NSBB (propranolol (nadolol/carvedilol)) and suggests NSBB as first line. VBL if contraindications of NSBB



[1] National Institute for Health and Care Excellence
[2] The British Society of Gastroenterology

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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

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Internal Pilot Trial (Jan 22 – Jul 22)

Must meet the following targets to justify progression:

>400 participants

>74 sites

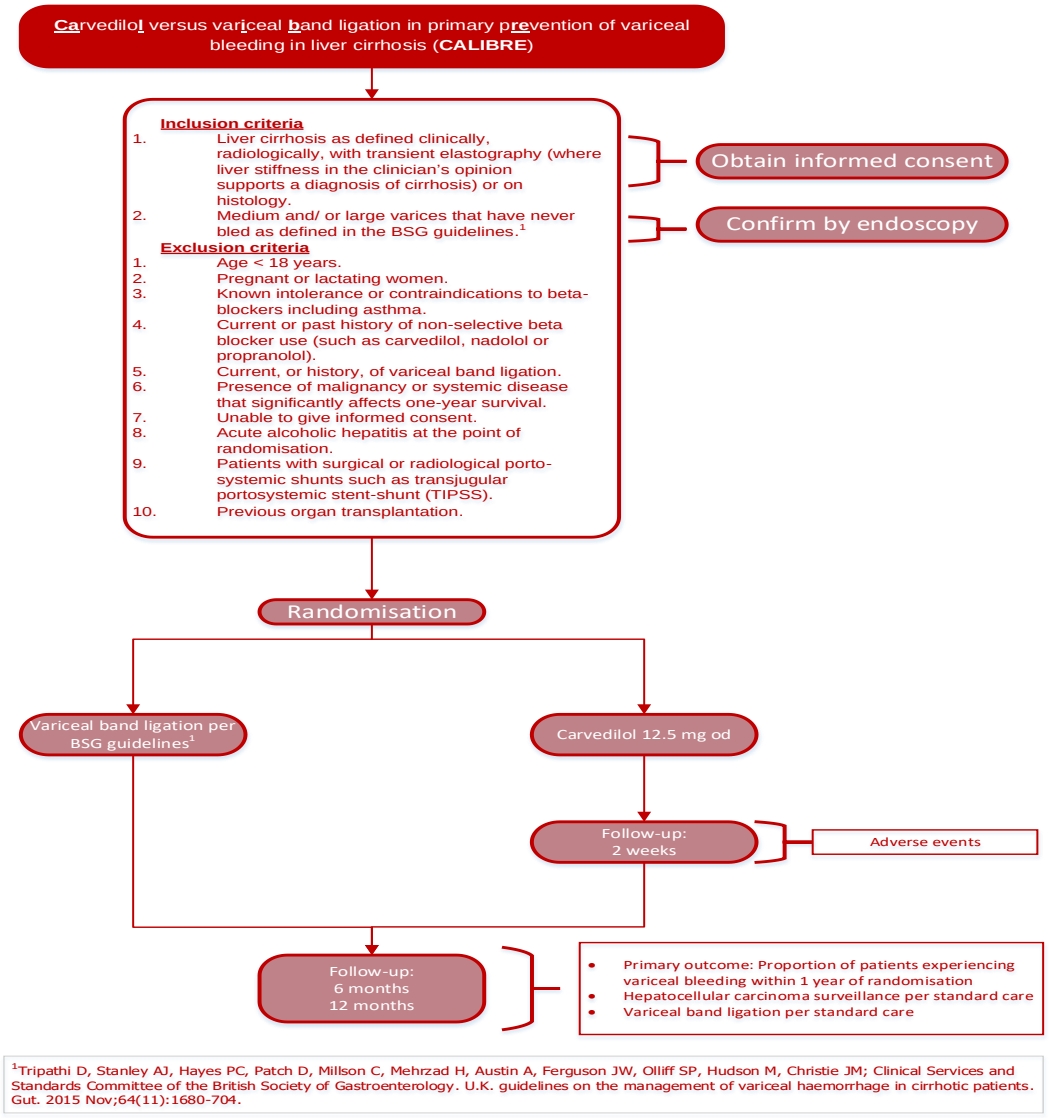
1 patient per month per open site

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



[1]Tripathi 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 port-systemic shunts such as tranjugular portosystemic stent-shunts (TIPSS)

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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

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Figure 1: Protocol V.3.0 page 32

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

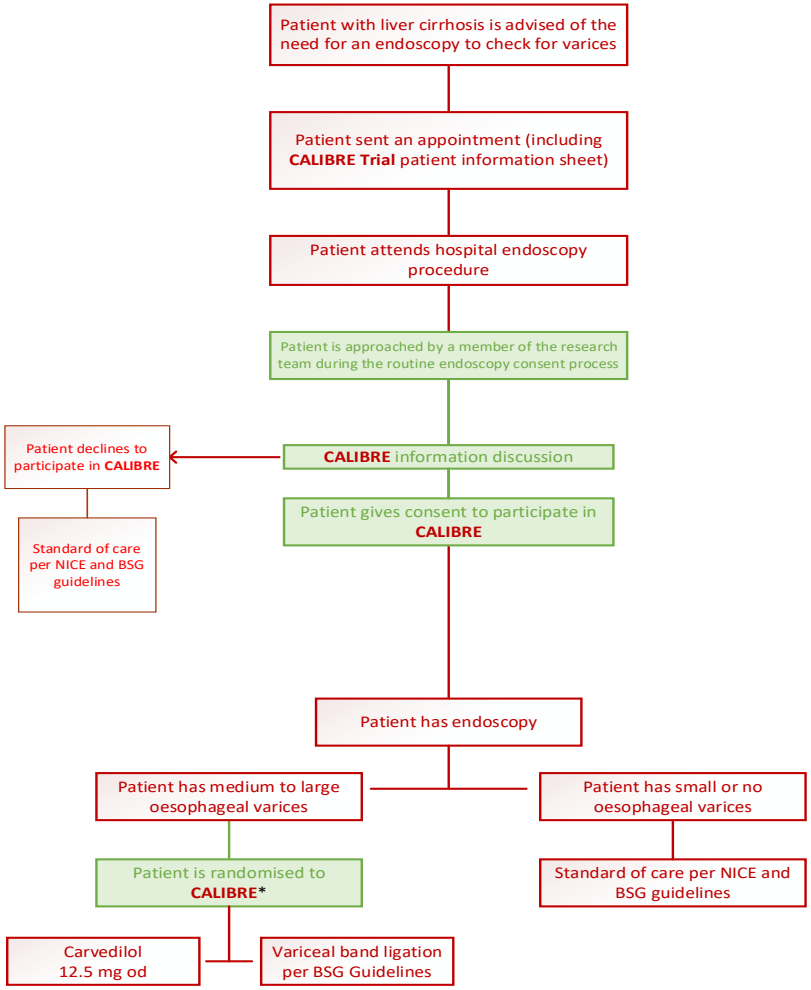
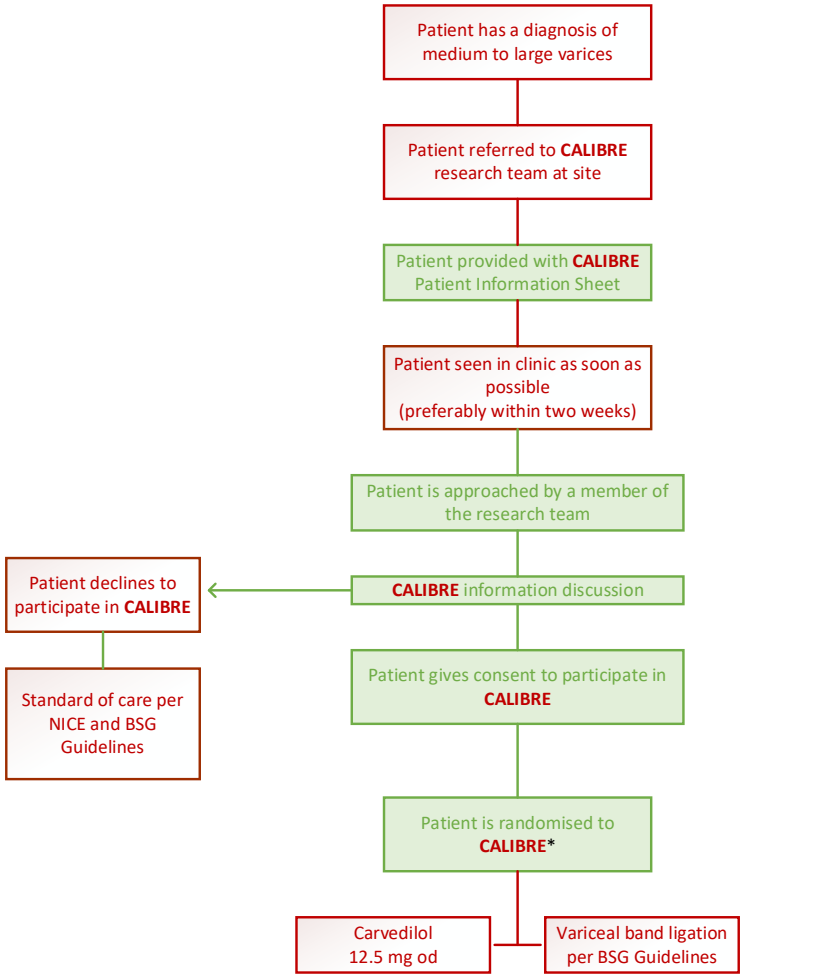


Figure 2: Protocol V.3.0 page 33

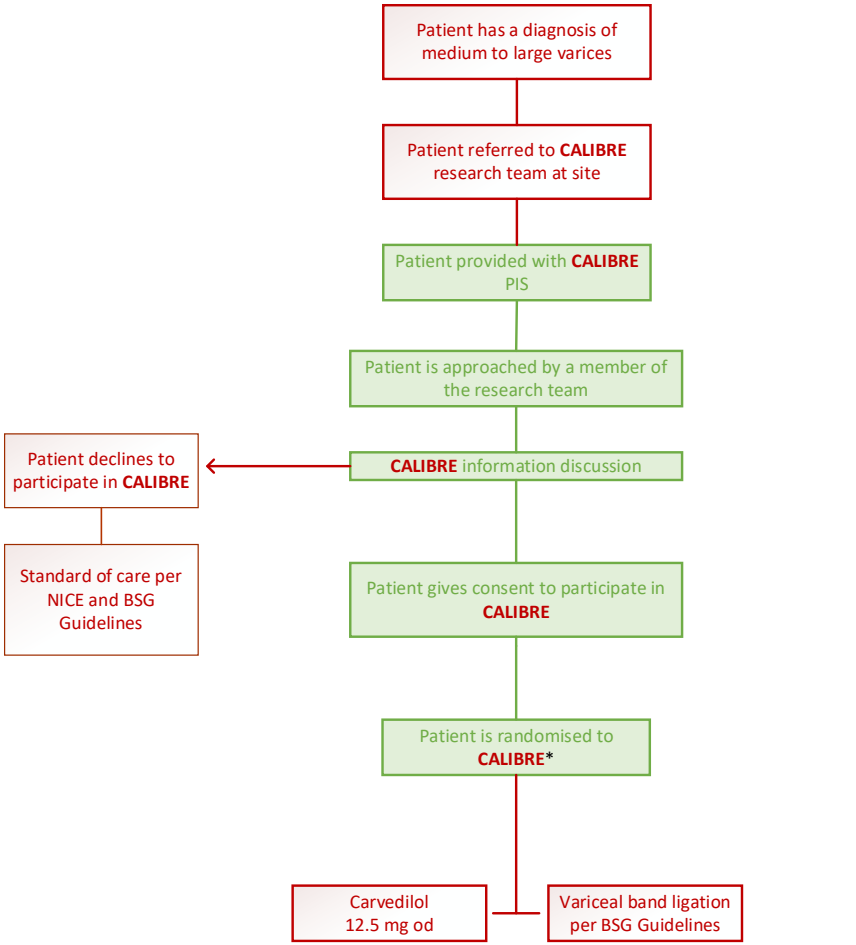
Consent process following referral from an outpatient clinic following diagnostic endoscopy



**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).*

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 guidelines and/ or local policies).*

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

Example ICF

TO BE PRINTED ON LOCAL TRUST HEADED PAPER

Informed Consent Form

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

Site name: University Hospital Birmingham **Principal Investigator:** Neil Rajoriya

Participant Trial Number: 0 1 1 1 **Please initial each box to confirm consent ↓**

1. 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. LH
2. 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. LH
3. 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 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 my records. LH
4. 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. LH
5. Information collected that identifies me by name, e.g. consent forms as well as contact address 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. LH
6. To permit the accurate follow-up of all participants it may be necessary for the **CALIBRE Study** 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
7. I agree to take part in the **CALIBRE Study**. LH

To continue participating in the CALIBRE Study you MUST consent to points 1-7 above and initial the corresponding boxes.
A witness is mandatory for remote consent.

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

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

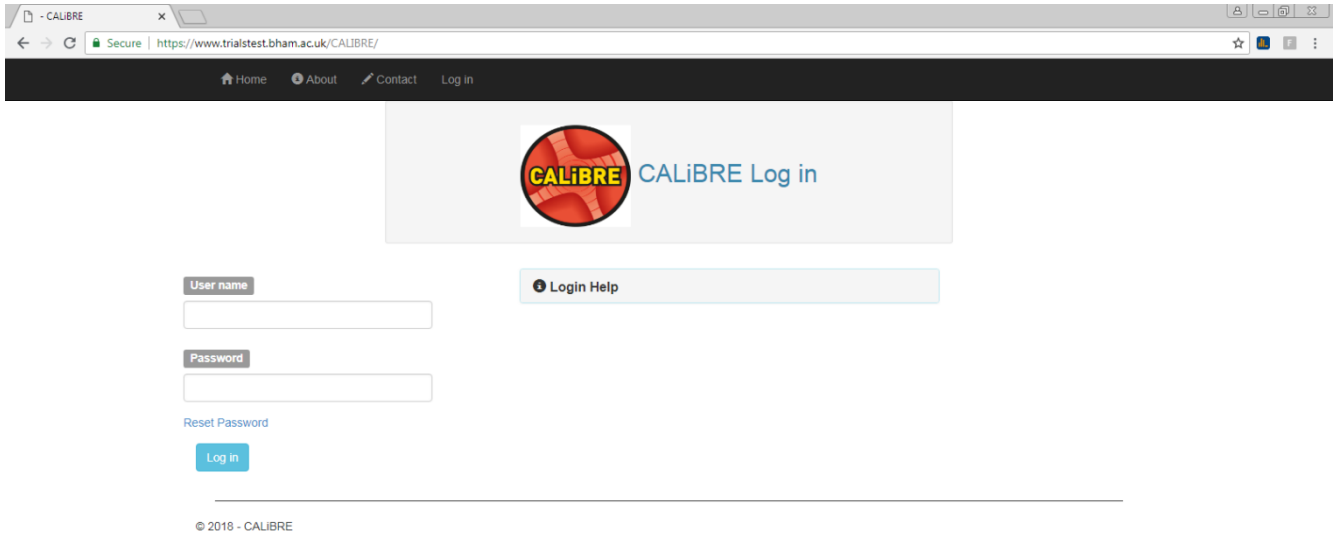
Randomisation cont.

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

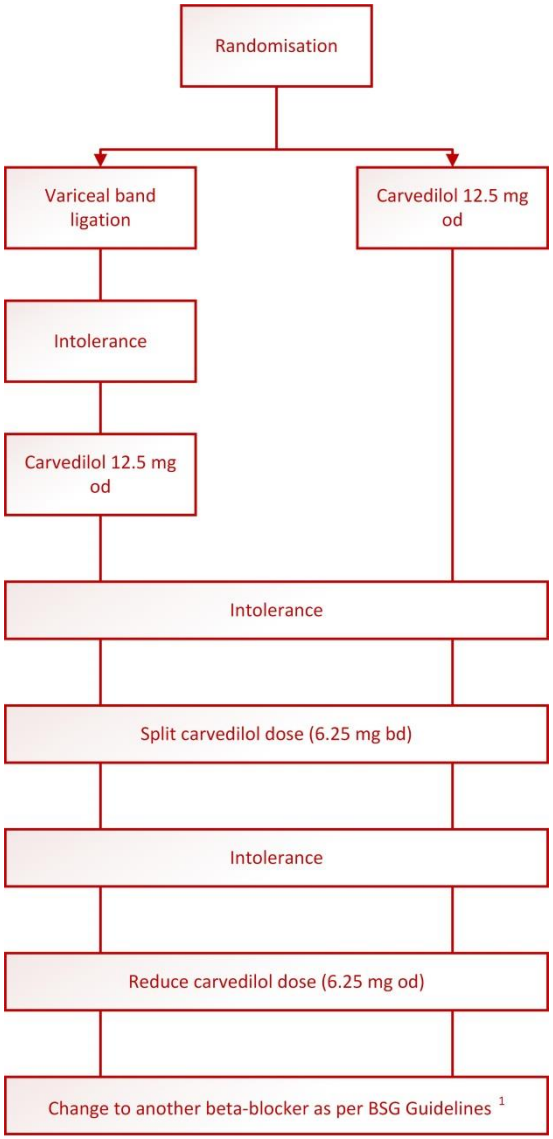
Carvedilol:

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[¥] ± 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		✓	✓	✓
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.

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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

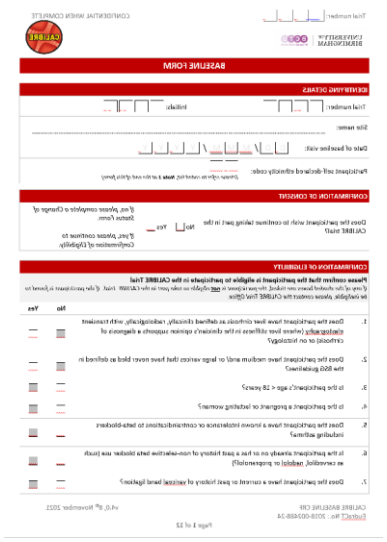
Case Report Forms

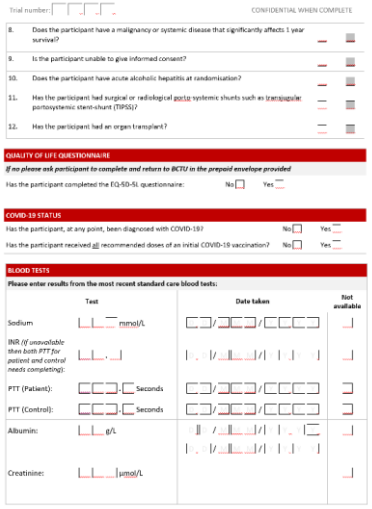
CRFs will be paper records completed on site

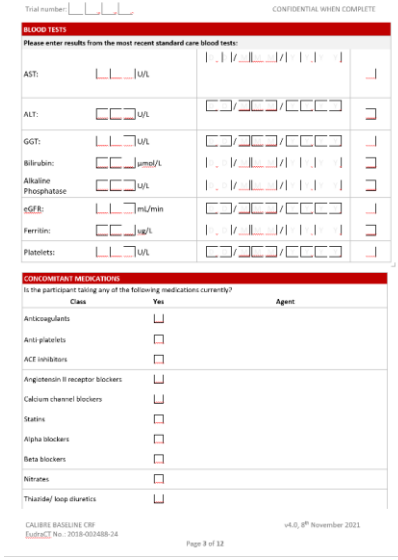
CRFs are considered complete when all data fields are completed unambiguously or the data is marked as unobtainable

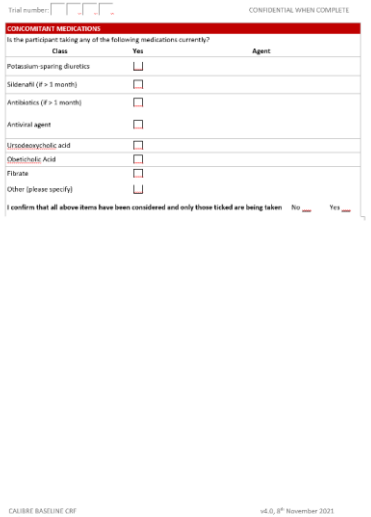
The original or copy of each completed CRF should be sent to BCTU, and a true copy filed in the ISF

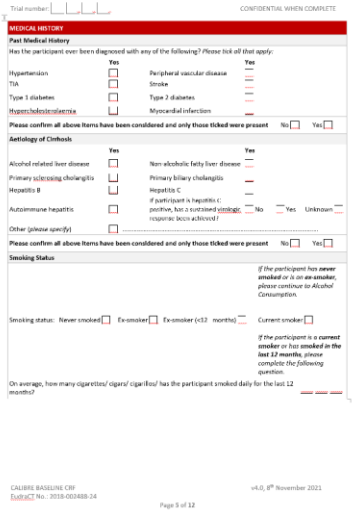
Case Report Forms - Baseline

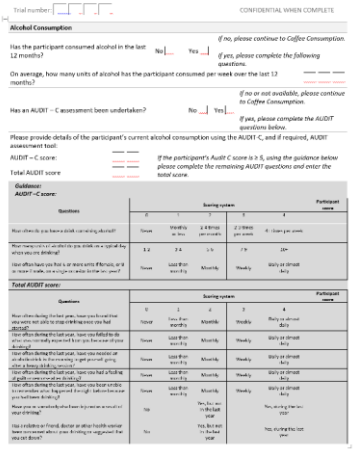


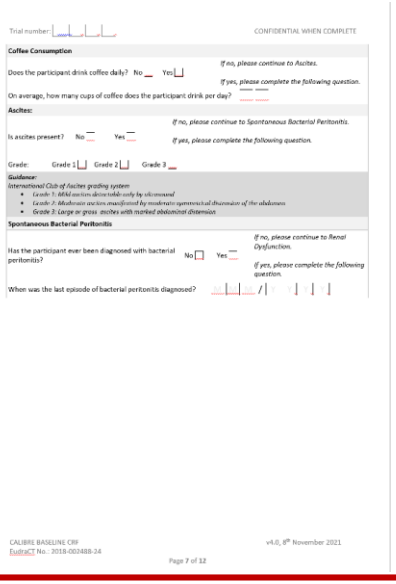


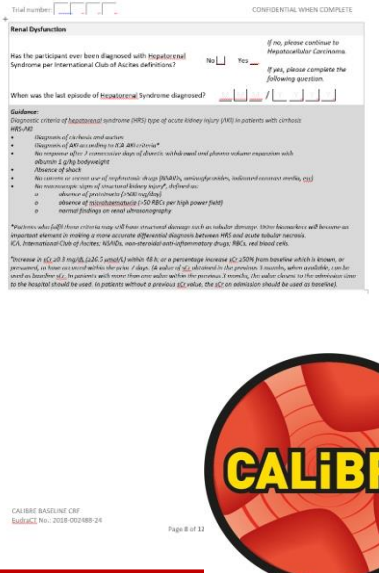












Version Control CRFs

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 SmPC[1] or the IB[2] for that product

[1] 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

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Reporting

Serious but listed on page 46 of the protocol as expected

Follow up CRFs

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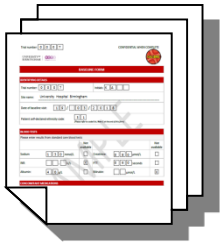
DMEC

MHRA

REC

Serious and NOT listed in protocol as expected

Fax or Email SAE Form within 24 hours



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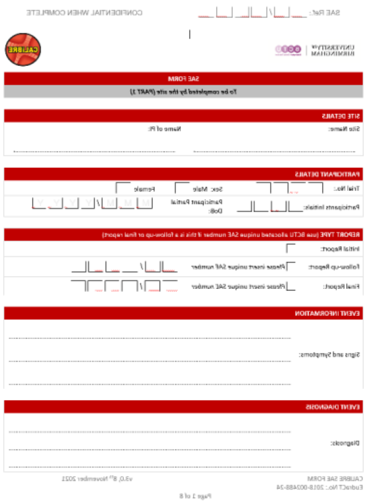
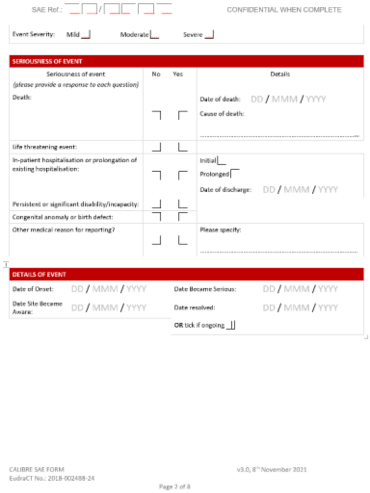
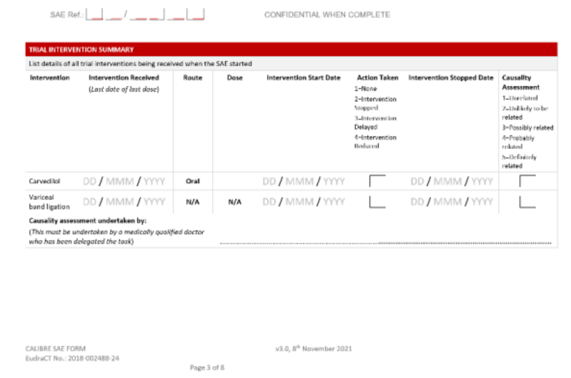
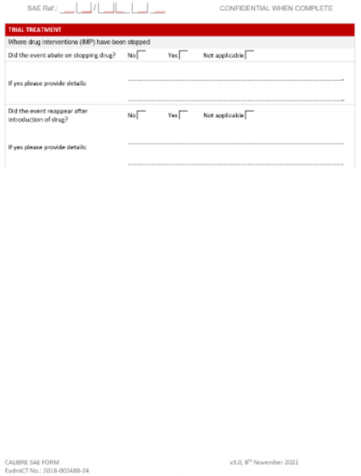
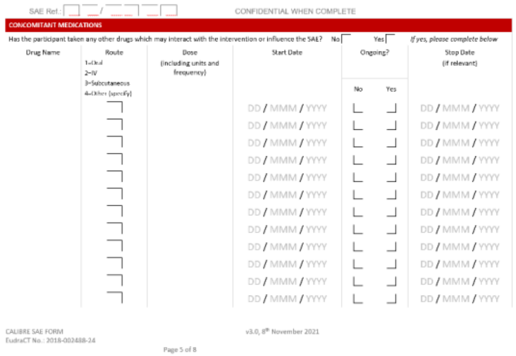
Example SAE Form

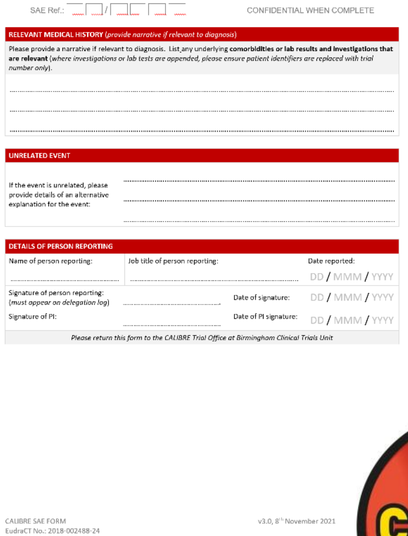












Urgent Reports

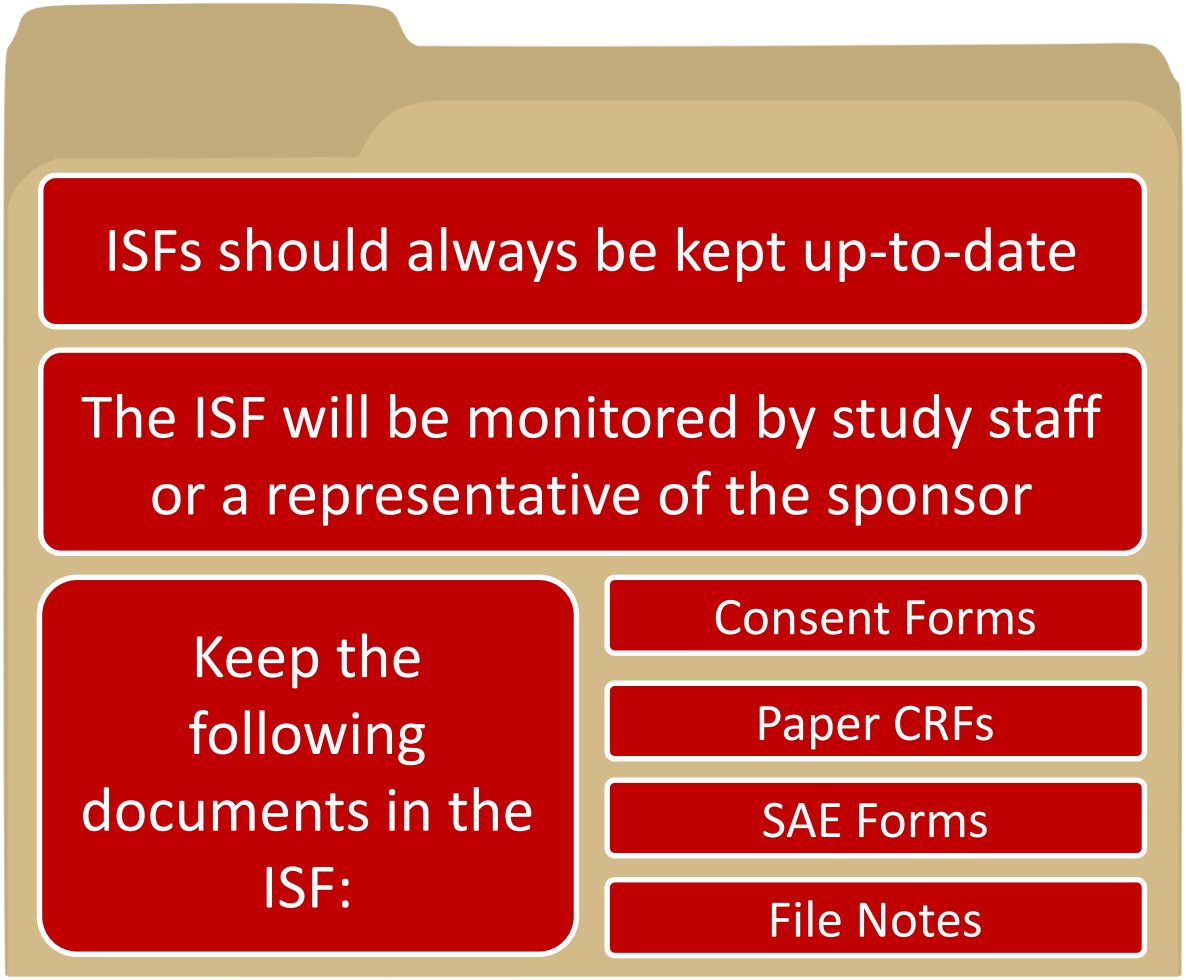
All expedited SAEs and SUSARs **must** be reported to BCTU **within 24 hours** of the site being made aware of the event

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



Contact Details

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0121 415 8445

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0121 415 9135

Email: calibretrial@trials.bham.ac.uk

Website: www.birmingham.ac.uk/calibretrial

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College of Medical and Dental Sciences
Public Health Building
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Edgbaston
Birmingham
B15 2TT

QUESTIONS