An Adaptive-Design Randomised Placebo-Controlled Trial of Baclofen in the Treatment of Alcohol Use Disorder in Patients with Liver Cirrhosis

BASIS Protocol
V3.0, 25/08/2023

Study Sponsor

Liverpool University Hospitals NHS Foundation Trust

Prescot Street

Liverpool

L7 8XP

EudraCT number: 2022-000154-28

CTA Reference Number: 16993/0006/001-0001

ISRCTN: 42860

Research Ethics Ref: 150700

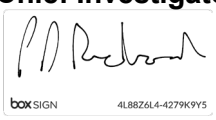
Sponsor Ref: R&I 6040

Funder Ref: NIHR131129

Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature: 

Date: 31 Aug 2023

Dr Paul Richardson
Consultant Hepatologist and Clinical Director Gastroenterology and Hepatology
Liverpool University Hospital Foundation Trust

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of Sponsor:

Signature: 

Date: 29 Aug 2023

Heather Rogers
R&I Governance Manager
Liverpool University Hospital Foundation Trust

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of the Lead Statistician:

Signature: AP Jones **Date:** 29 Aug 2023

Dr Ashley Jones
Head of Statistics, Liverpool Clinical Trials Centre
University of Liverpool

General Information

This document describes the BASIS trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the coordinating centre (Liverpool Clinical Trials Centre; LCTC) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to Dr Paul Richardson & Prof Sir Munir Pirmohamed via the LCTC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 15.

The Liverpool Clinical Trials Centre (LCTC) brings together a wealth of expertise built on the experience of the Liverpool Trials Collaborative which has held full registration status with the UK Clinical Research Collaboration CTU network since its establishment in 2007 (www.ukcrc.org). The LCTC has a diverse trial portfolio underpinned by methodological rigour, a Good Clinical Practice (GCP) compliant data management system, and core standard operating procedures.

Randomisation: web access http://www.basis-study.com

If there are any problems with the randomisation systems contact

LCTC on 0151 794 0249 or via email on basis@liverpool.ac.uk

(Note that the LCTC is open from 0900 – 1700, Monday – Friday, excluding public holidays and University of Liverpool closed days)

Clinical Queries

Clinical queries relating to this trial should be referred to the Chief Investigator, Dr Paul Richardson & Prof Sir Munir Pirmohamed, via the LCTC basis@liverpool.ac.uk.

SAE Reporting

Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible investigator and submitted to **LCTCSafe@liverpool.ac.uk** within 24 hours of becoming aware of the event (See section 12 for more details).

Contact Details: Institutions		
Sponsor:	**Trial Management, Monitoring and Analysis:**	**Clinical Laboratory (data analysis):**
Liverpool University Hospitals NHS Foundation Trust Prescot Street Liverpool L7 8XP RGT@RLBUHT.nhs.uk	**Liverpool Clinical Trials Centre** University of Liverpool Liverpool L69 3BX +44(0)151 794 0249 basis@liverpool.ac.uk	**Antimicrobial Pharmacodynamics and Therapeutics Group (APT)** **Institute of Systems, Molecular & Integrative Biology** 1st Floor William Henry Duncan Building 6 West Derby Street University of Liverpool Liverpool L7 8TX +44(0)151 7957648
IMP Manufacturing and Supply:	**Clinical Laboratory (sample kits production):**	
Royal Free Specials Pharmaceuticals Pond Street, London, NW32QG	**GCP Laboratory Facility** **(GCP Lab)** 2nd Floor William Henry Duncan Building 6 West Derby Street University of Liverpool Liverpool L7 8TX +44(0)151 794 8373	

Contact Details: Individuals		
Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**	**Co-Lead Investigator:**
Mrs Heather Rogers R&I Governance Manager Tel: 0151 706 3702 Fax: 0151 706 3703 RGT@liverpoolft.nhs.uk	**Dr Paul Richardson** Consultant Hepatologist Dept. Divisional Medical Director Royal Liverpool University Hospital NHS FT Tel: 0151 706 3568 Paul.Richardson@liverpoolft.nhs.uk	**Prof Sir Munir Pirmohamed** David Weatherall Chair of Medicine and NHS Chair of Pharmacogenetics Institute of Systems, Molecular and Integrative Biology (ISMIB) University of Liverpool Tel: 0151 794 5549 munirp@liverpool.ac.uk
Additional Medical Expert who will Advise on Protocol Related Clinical Queries:	**Sponsor Representative for Pharmacy/Clinical Trials Supplies**	
Dr Michael Allison Consultant Hepatologist Cambridge University Hospitals NHS Foundation Trust Hills Road Cambridge CB2 0SP Tel: 01223 245151 michael.allison@addenbrookes.nhs.uk	Ms Rebecca Tangney **c/o** R&I Governance Manager Tel: 0151 706 3702 Fax: 0151 706 3703 rebecca.tangney@liverpoolft.nhs.uk	

Additional Contacts:

The contact details for the trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File

1 Table of Contents

2 Glossary

AASLD	American Association for the Study of Liver Diseases
AE	Adverse Event
AR	Adverse Reaction
APQ	Alcohol Problems Questionnaire
AUD	Alcohol Use Disorder
AUDIT	Alcohol Use Disorders Identification Test
CHI	Community Health Index
CI	Chief Investigator
C-SSRS Screen	Columbia -Suicide Severity Rating Scale Screen
CTA	Clinical Trial Authorisation
CTFG	Clinical Trial Facilitation Group
CTIMP	Clinical Trials of an Investigational Medicinal Product
CTU	Clinical Trials Unit
EASL	European Association for the Study of the Liver
eCRF	electronic Case Report Form
eDRIS	electronic Data Research and Innovation Service
EUDRACT	European Clinical Trials Database
FDA	Food and Drug Administration (US)
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
IB	Investigator's Brochure
ICD	International Classifications of Disease
IDSMC	Independent Data and Safety and Monitoring Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
IWRS	Interactive Web Response System
LCTC	Liverpool Clinical Trials Centre
LC-MS	Liquid chromatography-mass spectrometry
MA	Marketing Authorisation
MELD-Na	Model for end-stage liver disease
MHRA	Medicines and Health Care products Regulatory Agency
NHS	National Health Service
NIHR CRN	National Institute for Health Research Clinical Research Network
NICE	The National Institute for Health and Care Excellence
NRES	National Research Ethics Service
ONS	Office for National Statistics
PACS	Penn Alcohol Cravings Scale
PBPP-HSC	Public Benefit and Privacy Panel for Health and Social Care
PI	Principal Investigator
PK/PD	Pharmacokinetic/Pharmacodynamic
PSF	Pharmacy Site File
QA	Quality Assurance
QC	Quality Control
Q-F	Quantity and Frequency (units of alcohol consumption)

R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
RSO	Research Support Office
SADQ	Severity of Alcohol Dependence Questionnaire
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDS	Three time daily
TIPS	Trans-jugular intrahepatic porto-systemic shunt
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
WOCBP	Women of Childbearing Potential

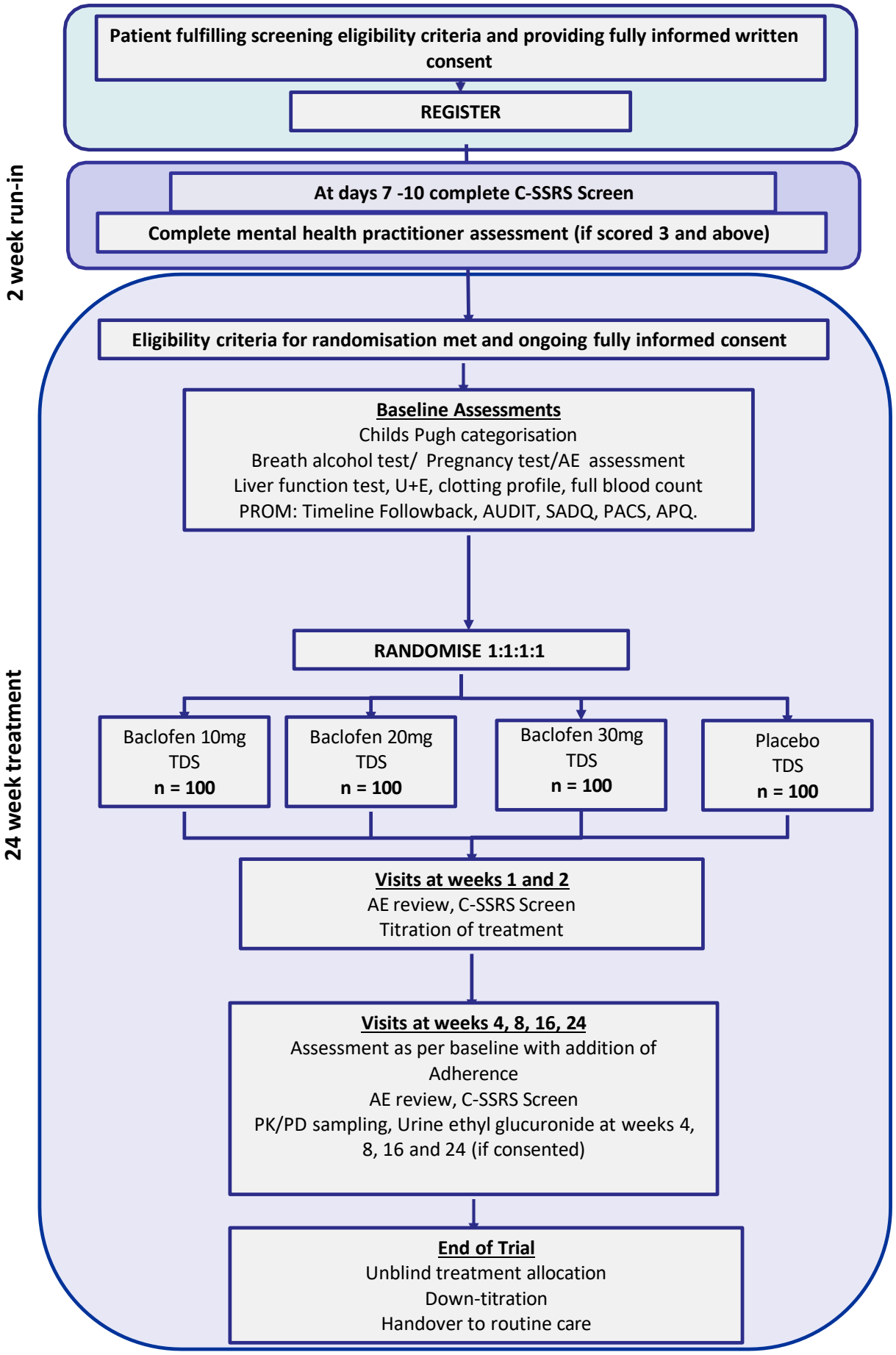
3 Protocol Overview

Full Title:	An adaptive-design randomised placebo-controlled trial of baclofen in the treatment of alcohol use disorder in patients with liver cirrhosis
Acronym:	BASIS
Phase:	III
Target Population:	We will target patients managed in a secondary and tertiary care setting that have a confirmed diagnosis of alcohol related cirrhosis. The patients will be aged 18- 65 years and there will be no preference for sex or ethnicity.
Sample size:	400
Eligibility criteria at REGISTRATION	**Inclusion Criteria at Registration** 1. Age 18 to 65 years 2. Confirmed diagnosis of alcohol-related cirrhosis classified according to the Child-Pugh classification 3. Abstinent from alcohol at the time of registration for between ≥1 day and <42 days 4. Capacity to provide informed consent **Exclusion Criteria at Registration:** 1. Planning to become pregnant, is pregnant or breastfeeding 2. Overt hepatic encephalopathy or Trans-jugular intrahepatic porto-systemic shunt in situ 3. Severe renal impairment (stage 5 Chronic Kidney Disease and/or current haemodialysis) 4. History of illicit drug excluding marijuana use in the previous 4 weeks 5. Concurrent use of opioid substitution therapy 6. Use of licenced alcohol anti-craving pharmacotherapy (such as acamprosate, disulfiram naltrexone, nalmefene) in previous 12 weeks 7. Use of baclofen for any purpose in previous 12 weeks 8. Peptic ulceration detected by endoscopy within 14 days of registration. 9. Known hypersensitivity to baclofen or structurally related drugs or any other component of the formulation. 10. Poorly controlled major psychiatric disorder such as schizophrenia or bi-polar disorder 11. Individuals who have participated in a trial of a medicinal product within 12 weeks preceding registration 12. Poorly controlled epilepsy 13. Rare hereditary problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption 14. Suffering from Porphyria

Eligibility criteria at RANDOMISATION	**Inclusion Criteria at Randomisation:** 1. Age 18 to 65 years 2. Confirmed diagnosis of alcohol-related cirrhosis classified according to the Child-Pugh classification 3. Abstinent from alcohol at the time of the baseline/ randomisation visit for between ≥14 days and <56 days 4. Capacity to provide informed consent 5. Women of reproductive potential must have a negative pregnancy test at randomisation and use highly effective contraception for the duration of the treatment period. **Exclusion Criteria at Randomisation:** 1. Planning to become pregnant, is pregnant or breastfeeding 2. Overt hepatic encephalopathy or Trans-jugular intrahepatic porto-systemic shunt in situ 3. Severe renal impairment (stage 5 Chronic Kidney Disease and/or current haemodialysis) 4. History of illicit drug use excluding marijuana in the previous 6 weeks 5. Concurrent use of opioid substitution therapy, or use in the previous 14 days 6. Use of licenced alcohol anti-craving pharmacotherapy (such as acamprosate, disulfiram naltrexone, nalmefene) in previous 14 weeks 7. Use of baclofen for any purpose in previous 14 weeks 8. Peptic ulceration detected by endoscopy within 28 days of the baseline/randomisation visit. 9. Known hypersensitivity to baclofen or structurally related drugs or any other component of the formulation 10. Scored 3 or more on the C-SSRS Screen and has been assessed by an appropriately qualified mental health practitioner as having suicidal ideation or behaviour prior to the baseline/randomisation visit 11. Poorly controlled major psychiatric disorder such as schizophrenia or bi-polar disorder 12. Individuals who have participated in a trial of a medicinal product within 14 weeks preceding the baseline/randomisation visit 13. Poorly controlled epilepsy 14. Rare hereditary problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption 15. Suffering from Porphyria
Study Centres and Distribution:	UK NHS Secondary and Tertiary Care Providers Please refer to section 6.2

Patient Study Duration:	Duration of active participation is a maximum of 26 weeks: Trial registration and a 2-week run-in Maximum of 24 weeks of active treatment ONS death data may be collected at the end of the study	
Study Duration	48 months	
IMP / Intervention:	**Intervention:**	
	IMP:	Baclofen
	Form:	Tablet
	Dose:	30mg per day / 60mg per day / 90mg per day
	Route:	Oral
	Control:	
		Matching placebo administered as per IMP
Objectives:		
Primary:	To investigate the effect of baclofen compared with placebo in the treatment of AUD in patients with alcohol-related cirrhosis	
Secondary:	1) To determine if the treatment of AUD with baclofen in patients with alcohol-related cirrhosis is superior to placebo. 2) To determine which dose(s) of baclofen is/are most effective in improving AUD treatment outcomes in patients with alcohol-related cirrhosis in comparison to placebo 3) To assess the relationship between variability in baclofen exposure and efficacy and safety parameters. 4) To monitor and compare the safety profile of the baclofen arms, including dose dependency, in comparison to the placebo arm	

3.1 Schematic of Study Design



4 Roles and Responsibilities

Sponsor

The Liverpool University Hospitals NHS Foundation Trust is legally responsible for the study. They will formally delegate specific Sponsoring roles to the Chief Investigator and Clinical Trials Unit.

Funder

This study is funded by the National Institute for Health Research, Health Technology Assessment programme.

Funder	Financial and Non-financial Support Given	Role
NIHR Health Technology Assessment Programme	Financial support for the delivery of the project	This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results for publication or other dissemination.

Chief Investigator: Dr Paul Richardson is the Chief Investigator (CI) and Prof Sir Munir Pirmohamed is the Co-Lead Investigator for the trial and are responsible for the overall design and conduct of the trial in collaboration with other members of the study team.

Principal Investigators: In each participating centre a principal investigator will be identified to be responsible for identification, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

Clinical Trials Unit: (LCTC) at the University of Liverpool in collaboration with the Chief Investigator and Co-Lead Investigator will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, budget administration, LCTC Trial Master File management, safety reporting, data management, randomisation, statistical analysis, participating site coordination and oversight of IMP distribution.

Oversight Committees

The BASIS trial is subject to oversight from the following committees:

Trial Management Group (TMG)
A Trial Management Group (TMG) will be formed comprising the Chief Investigators, other lead investigators (clinical and non-clinical), members of the LCTC, and PPI representation. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management of the trial. The TMG will meet regularly in accordance with their terms of reference.

Trial Steering Committee (TSC)
The Trial Steering Committee will consist of an independent chairperson, and additional independent experts in the field of hepatology/pharmacology, biostatistician and will include the joint-CIs and observers. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The decision for the continuation of the trial lies with the TSC and as such they will meet throughout the trial (at least annually).

Independent Data and Safety Monitoring Committee (IDSMC)
The IDSMC will consist of at least three independent members encompassing expertise in biostatistics, hepatology and pharmacology.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. They will review data during closed meetings and make recommendations to the TSC concerning the continuation of the study.

The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in Section 13.3 and 14.3 respectively.

5 INTRODUCTION

5.1 Background

The BASIS trial will explore the efficacy of different doses of baclofen for the treatment of alcohol use disorder in patients with alcohol-related cirrhosis. Baclofen is a well-established anti-spasticity therapy (1). More recently, the drug has been considered as a promising alcohol anti-craving agent in the treatment of AUDs. It has the advantage of being predominantly excreted via the kidneys (~85%) and thus is likely to be relatively safer than other alcohol anti-craving medication in patients with established liver disease. The pace at which baclofen was adopted in clinical practice for AUD, particularly in France, has resulted in wide variation in practice, particularly in relation to maximum dose used. Meta-analysis supports the use of lower dose baclofen to improve drinking outcomes in patients with AUD (2, 3). However, there is a paucity of data in patients with advanced liver disease and many studies exceed the 100 mg/d cut-off established in NICE guidelines for spasticity. Furthermore, recent findings suggest potential safety concerns at higher doses (4).

Initial randomised placebo-controlled trials of baclofen in patients with alcohol dependence in the presence or absence of liver cirrhosis utilised a dose of 30 mg/d, with both positive (5, 6) and null outcomes (7). Animal models (8) and anecdotal reports (9, 10) proposed that baclofen's efficacy may be dose-dependent, with higher doses potentially improving outcomes. A placebo-controlled trial conducted in Germany individually titrated participants with AUD (no liver cirrhosis patients) based on effectiveness to a maximum dose of 270 mg/d (mean dose 180 mg/d) (11). The active treatment group reported greater total and cumulative abstinence. A recent RCT conducted in primary care in France, with AUD patients titrated according to response to a maximum of 300 mg/d, reported increased rates of abstinence in the final month of treatment (primary outcome), although many other measures did not demonstrate a clear effect. Two other trials using maximum doses of 150 mg/d and 180 mg/d returned null outcomes (12, 13). Higher doses have also been linked to increased risk of adverse events such as sedation (14) and most studies have omitted patients with severe liver disease.

The efficacy and safety of baclofen in AUD patients with advanced liver disease was first tested in a double-blind, placebo-controlled clinical trial, with 84 AUD patients with liver cirrhosis being randomised to baclofen treatment (30 mg/d) or placebo (6). The proportion of patients with total alcohol abstinence (71% allocated baclofen, 29% allocated placebo; OR=6.3; p=0.0001) and cumulative abstinence duration (mean 62.8 [SE 5.4] vs. 30.8 [5.5]; p=0.001) was significantly higher in the baclofen group. In the BacALD study, 104 patients with AUD were enrolled, including 58 with alcohol-related liver disease (15). Patients were administered one of two fixed doses of baclofen (30 or 75 mg/d) or placebo. Compared with placebo, significant efficacy of baclofen on time to lapse ($\chi 2 = 6.44$, $P < 0.05$, Cohen's $d = 0.56$) and to relapse ($\chi 2 = 4.62$, $P < 0.05$, $d = 0.52$) was found, with no difference between the two doses of baclofen. Our own cohort study in 219 patients with varying severities of liver disease, including cirrhosis, found baclofen administration (up to 90 mg/d) had a positive impact on measures of alcohol consumption (e.g. after 12 months, 53% of patients with follow-up data were abstinent) and adherence was high (16). No other studies have explored baclofen for AUD treatment in patients with liver cirrhosis.

5.2 Rationale

Our current understanding of the relationship between baclofen dose and exposure in the AUD population is poor. This is further compounded by potential inter-individual variability in drug exposure and metabolism (17-19). A small-scale pharmacokinetic/dynamic modelling study in baclofen reported that dose and duration of exposure might be important factors in response (20). A later study in 143 alcohol-dependent individuals using baclofen doses ranging from 15 to 250 mg/d showed a proportional relationship between oral dose and plasma baclofen exposure (19). However, interindividual variation was not corrected by

adjustment for demographic or clinical covariates. The study also recruited few patients with liver disease and the severity of any disease was mild. A pharmacodynamic model used the Obsessive-Compulsive Drinking Scale (21) as a measure of baclofen's effectiveness in 50 patients (22). This study revealed that some patients needed a higher dose or longer duration to respond. Non-responders were more likely to have higher creatinine and alkaline phosphate levels, suggesting that impaired liver and/or kidney function might modulate response to baclofen. Further studies utilising more sophisticated PK/PD modelling in patients with different degrees of liver and renal impairment are needed. These will determine the relationships between exposure and pharmacodynamic response. This is especially important in patients with alcohol-related cirrhosis where response (i.e. abstinence) is directly linked to prognosis (23).

Thompson et al. have performed a systematic review of prescribing practices for baclofen in AUD treatment in observational studies (24). Twenty-five relevant studies reporting outcomes in 613 patients were identified. Starting doses ranged between 5 and 50 mg/d. Titration was study-dependent, and doses were increased until either therapeutic target, such as abstinence or study-defined low risk drinking, was achieved or adverse events resulted in a dose reduction or discontinuation. The maximum dose for individual patients ranged between 20 and 630 mg/d. In studies with 10 or more patients, a negative correlation was found between dose and proportion of patients achieving the therapeutic goal. It was concluded that prescribing practices are 'haphazard', and definitive evidence for appropriate dosing and clinical effectiveness is required.

A search on clinicaltrials.gov (conducted 29/09/2022) identified no other currently recruiting trials with an overlapping design. One recently completed 3-arm trial in AUD patients was identified where baclofen doses of 30 and 90 mg/d were compared alongside a placebo (NCT01980706). However, patients with alcohol related liver disease were not included. Data posted on the primary outcome (percent heavy drinking days) suggests a positive effect of the 90 mg/d dose compared with placebo.

Why this research is needed now

Continued alcohol consumption in patients with established cirrhosis accelerates the time to death, with the 5-year survival rate being 12% lower in those who continue drinking (25). Such figures reinforce the need for abstinence in patients with alcohol-related cirrhosis. The question "What are the most effective ways to help people with alcohol-related liver disease stop drinking?" is considered a top priority by the James Lind Alliance. The need is also highlighted in recent guidance updates from American Association for the Study of Liver Diseases (AASLD) who stated, "Studies are needed to assess the efficacy of psychosocial and pharmacological treatments in initiating and maintaining abstinence by patients with alcohol-related liver disease".

Alcohol-related illness places an enormous burden on the NHS. A National Confidential Enquiry into Patient Outcome and Death report highlighted the poor standard of care for patient's admitted to secondary care with alcohol-related liver disease (26). Furthermore, the Lancet Liver Commission recently questioned whether improvements have been made, or at least at an appropriate pace (27).

Currently approved pharmacological treatments for AUDs in patients with cirrhosis are either unsuitable due to primary liver metabolism (i.e. disulfiram, naltrexone, and nalmefene) or are incompletely evaluated (i.e. acamprosate). This creates clinical uncertainty and consequently, variation in access to pharmacotherapy. Globally, per capita alcohol consumption is expected to rise until at least 2030, especially in middle income countries (28). This is likely to increase the burden of cirrhosis, particularly when considered alongside rising obesity rates (29). Therefore, there is a pressing need to generate high quality data from RCTs to enable the development of robust clinical pathways for the effective management of AUD in patients with cirrhosis. This will lead to greater access to treatment, reduce variability in patient management and standardise care pathways.

5.3 Risk and Benefits

Potential Risks

Baclofen has a well-established safety profile, with known adverse effects documented (30). Furthermore, the doses to be used consider the evidence from trials, personal experience as presented in Owens et al (20), and the upper limit of baclofen dosing in the UK (100 mg/day). Specific exclusion criteria have been adopted to minimise the risk of serious adverse events in certain groups (see section 7 for details). In addition, suicide and suicide-related events have been reported in patients treated with baclofen. In most cases, the patients had additional risk factors associated with an increased risk of suicide including alcohol use disorder. The requirement for abstinence prior to recruitment will mitigate this risk. Patients assessed by a mental health practitioner to be at risk of suicide prior to the randomisation visit will be excluded. Participants will be alerted about the need to monitor for suicidal thoughts and to seek medical advice immediately if these symptoms present. Participants who score 3 and above on the follow up Columbia - Suicide Severity Risk Scale Screen (C-SSRS Screen) will need to discontinue treatment and will be unblinded and down-titrated.

Potential Benefits

Alcohol consumption in the presence of liver cirrhosis leads to poorer patient outcomes in comparison to patients who remain abstinent. Currently there are limited pharmacological options to promote abstinence in this patient group. Continued alcohol ingestion increases the risk of progressive liver failure and portal hypertensive bleeding (31) and reduces both short and long-term survival. The prognosis for patients with alcohol-related cirrhosis is extremely poor, with mortality rates of 71% at 5 years and 91% at 15 years for patients who continue to drink (32). Abstinence is associated with a ~40% reduced risk of mortality from 18 months onwards. Based on the effect size, we would expect an additional 25% of patients attending secondary care with co-occurring AUD and liver cirrhosis to have a ~40% reduced risk of death in the proceeding 5 years and potentially beyond. Importantly, death from alcohol-related cirrhosis usually occurs in people of working age. In 2015, more than one million years of life before the age of 50 were lost in Europe due to cirrhosis, with alcohol as the primary aetiology (33). Such premature deaths have a large impact on societies and economies. Despite shorter life expectancy, patients admitted with alcohol-related cirrhosis incur substantial costs for healthcare systems. The mean annual hospital costs for a person with alcohol-related liver disease is ≥10-fold higher than an age and sex matched person without alcohol-related liver disease (34).

Summary of benefit-risk profile

Considering the overall risk-benefit profile using the information outlined here, we consider that continued alcohol consumption in patients with liver cirrhosis to be a greater risk to future health than the risks posed by baclofen use. This trial is categorised as Type A (No higher than the risk of standard medical care) as per the risk-adapted approach to clinical trials adopted by the MHRA. More detail regarding management of risks associated with this trial are detailed in a separate Risk Assessment maintained in the Trial Master File.

5.4 Objectives

Primary Objective

The primary objective is to investigate the effect of baclofen compared with placebo in the treatment of AUD in patients with alcohol-related cirrhosis.

Secondary Objective(s)

1. To determine if the treatment of AUD with baclofen in patients with alcohol-related cirrhosis is superior to placebo
2. To determine which dose(s) of baclofen is/are most effective in improving AUD treatment outcomes in patients with alcohol-related cirrhosis in comparison to placebo
3. To assess the relationship between variability in baclofen exposure and efficacy and safety parameters.
4. To monitor and compare the safety profile of the baclofen arms, including dose dependency, in comparison to the placebo arm

6 STUDY DESIGN

BASIS is a 26-week adaptive-design randomised controlled, double-blind, multi-centre four-arm trial of baclofen compared to placebo in patients with alcohol-related cirrhosis. Participants will be randomised (1:1:1:1 allocation ratio) to one of four possible arms (baclofen 10 mg TDS, baclofen 20 mg TDS, baclofen 30 mg TDS, placebo TDS). Randomisation will be equal between groups and stratified by severity of liver disease based on the three categorises of Child-Pugh and recruitment centre. All patients will receive hospital-level Standard of Care (SOC). The trial includes a 2-week pre-randomisation run-in period to account for non-treatment seeking individuals. We have selected an adaptive design to remove intervention arms that demonstrate poor effectiveness, thus improving trial efficiency (35). An internal pilot will be conducted to ensure trial feasibility and optimal delivery. An interim analysis is planned once the primary outcome has been observed for at least 50 patients in each arm. At this point any treatment that is worse or equal to the placebo group will be dropped. If all treatment arms are dropped then the trial will stop. If at least one experimental arm is continued, then a further 50 patients will be randomised to each remaining experimental arm along with 50 additional patients in the placebo arm. This strategy may reduce the required number of patients needed for the trial and is more efficient than a standard four arm trial.

6.1 Blinding

6.1.1 Who is blinded?

Knowledge of treatment allocation and dose will be restricted to those who have an explicit need to know this information in order to undertake their delegated function, for example statistician/s in LCTC involved in generation of randomisation lists.

Participants and site personnel, other than delegated pharmacy staff, will be blind to treatment and dose allocations, though individual allocation information can be disclosed where required, e.g. for immediate clinical need or for decisions about ongoing care at trial completion.

The Independent Data and Safety Monitoring Committee (IDSMC) will require access to treatment and dose allocations in order to fulfil their oversight obligations. This information will be shared confidentially.

6.1.2 How the blind will be maintained

Treatment will be supplied to sites as uniquely numbered bottles packaged and labelled such that they are indistinguishable as active doses of 10mg, 20mg or 30mg tablets or placebo tablets. Bottles will be assigned to participants in accordance with their randomised allocation of active/placebo and dose by the unblinded pharmacist.

Safety events will be reported in a blinded manner and unblinded for reporting of Suspected Unexpected Serious Adverse Reaction (SUSAR) to REC, MHRA and the IDSMC.

6.2 Study Setting

Participants will be identified and recruited from NHS organisations in the UK; a complete list of sites can be found in the Trial Master File (TMF). We anticipate that recruitment will occur either i) after admission to a secondary care setting under the care of a Hepatologist during a hospital spell in relation to their underlying liver disease, or ii) by the Alcohol Care Team contemporaneously managing the participants. Follow up will occur in NHS hospitals during in-patient stays or trial follow-up visits as outlined in section 10.8 and 10.9.

Selection of Participating Sites

Criteria for the selection of sites will be determined by the Trial Management Group and will be described in a separate document 'BASIS Site Suitability Assessment' maintained in the TMF.

The recruitment sites for the BASIS trial will be opened to recruitment upon successful completion of all global (e.g. REC and MHRA) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the LCTC. Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

Selection of Principal Investigators

Principal Investigators will have the medical expertise necessary to conduct the study in accordance to the protocol and all regulatory and ethical requirements. Written agreement to conduct research as such will be obtained prior to site initiation. A suitable co-investigator will be identified at each site to deputise in case of PI absence.

6.3 Internal Pilot

During the 9-month internal pilot phase we expect recruitment rates to average 1.87 patients per centre per month.

We will employ the following traffic-light stop/go criteria with regards proceeding to the full trial:

RED: Average recruitment rate falls below 0.94 patients per site per month or the number of sites opened is less than 5 – unless there are mitigating circumstances, determine that recruitment is not feasible and decide not to proceed;

AMBER: Average recruitment rate per site per month is between 0.94 and 1.87 or the number of sites opened is between 5 and 7 – Review recruitment strategies, report to TSC and NIHR HTA and continue with a modified recruitment strategy and intensive monitoring

GREEN: Average recruitment rate per site per month exceeding 1.87 and 8 sites opened– proceed with study. Following the pilot phase, the main phase will be completed within 24 months.

	Red	Amber	Green
Average Recruitment rate/site/month	<0.94	0.94 to 1.87	>1.87
Number of sites opened	< 5	5-7	8

7 ELIGIBILITY CRITERIA

All patients must provide written, informed consent before any study procedures occur (see Section 10.2 for more information regarding informed consent processes) and must meet all eligibility criteria as described below.

7.1 Eligibility Criteria at Registration

Inclusion Criteria at Registration

1. Age 18 to 65 years
2. Confirmed diagnosis of alcohol-related cirrhosis classified according to the Child-Pugh classification
3. Abstinent from alcohol at the time of registration for between ≥1 day and <42 days
4. Capacity to provide informed consent

Exclusion Criteria at Registration

1. Planning to become pregnant, is pregnant or breastfeeding
2. Overt hepatic encephalopathy or Trans-jugular intrahepatic porto-systemic shunt in situ
3. Severe renal impairment (stage 5 Chronic Kidney Disease and/or current haemodialysis)
4. History of illicit drug use excluding marijuana in the previous 4 weeks
5. Concurrent use of opioid substitution therapy
6. Use of licenced alcohol anti-craving pharmacotherapy (such as acamprosate, disulfiram naltrexone, nalmefene) in previous 12 weeks
7. Use of baclofen for any purpose in previous 12 weeks
8. Peptic ulceration detected by endoscopy within 14 days of registration.
9. Known hypersensitivity to baclofen or structurally related drugs or any other component of the formulation.
10. Poorly controlled major psychiatric disorder such as schizophrenia or bi-polar disorder
11. Individuals who have participated in a trial of a medicinal product within 12 weeks preceding registration
12. Poorly controlled epilepsy
13. Rare hereditary problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption
14. Suffering from Porphyria

7.2 Eligibility Criteria at Randomisation

Inclusion Criteria at Randomisation

1. Age 18 to 65 years
2. Confirmed diagnosis of alcohol-related cirrhosis classified according to the Child-Pugh classification
3. Abstinent from alcohol at the time of the baseline/randomisation visit for between ≥14 days and <56 days
4. Capacity to provide informed consent
5. Women of reproductive potential must have a negative pregnancy test at randomisation and use highly effective contraception for the duration of the treatment period

Exclusion Criteria at Randomisation

1. Planning to become pregnant, is pregnant or breastfeeding
2. Overt hepatic encephalopathy or Trans-jugular intrahepatic porto-systemic shunt in situ
3. Severe renal impairment (stage 5 Chronic Kidney Disease and/or current haemodialysis)
4. History of illicit drug use excluding marijuana in the previous 6 weeks
5. Concurrent use of opioid substitution therapy, or use in the previous 14 days
6. Use of licenced alcohol anti-craving pharmacotherapy (such as acamprosate, disulfiram naltrexone, nalmefene) in previous 14 weeks
7. Use of baclofen for any purpose in previous 14 weeks
8. Peptic ulceration detected by endoscopy within 28 days of the baseline/randomisation visit.
9. Known hypersensitivity to baclofen or structurally related drugs or any other component of the formulation
10. Scored 3 or more on the C-SSRS Screen and has been assessed by an appropriately qualified mental health practitioner as having suicidal ideation or behaviour prior to the baseline/randomisation visit
11. Poorly controlled major psychiatric disorder such as schizophrenia or bi-polar disorder
12. Individuals who have participated in a trial of a medicinal product within 14 weeks preceding the baseline/ randomisation visit
13. Poorly controlled epilepsy
14. Rare hereditary problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption
15. Suffering from Porphyria

7.3 Co-enrolment Guidelines

To avoid potentially confounding issues, participants must not be recruited into other CTIMP trials whilst taking part in BASIS. Where recruitment into a non-CTIMP trial is considered to be appropriate and without having any detrimental effect on the BASIS trial this must first be discussed with the LCTC who will contact the Chief Investigators (Dr Paul Richardson & Prof Sir Munir Pirmohamed).

8 TRIAL TREATMENT/ INTERVENTIONS

8.1 Introduction

Following run-in, eligible participants will be randomised (1:1:1:1 allocation ratio) to one of four possible arms (baclofen 10 mg TDS, baclofen 20 mg TDS, baclofen 30 mg TDS, placebo TDS). Blinded treatment bottles will be administered, with all participants blinded to both treatment and dose. The IMP will be manufactured by Tiofarma and re-packed, labelled and distributed by Royal Free Specials Pharmaceuticals in accordance with all applicable guidelines.

8.2 Treatment Name / Description

Treatment Arm - Baclofen

Brand name / Active ingredient:	Baclofen
Formulation:	10 mg, 20mg or 30mg oral tablet. Each dose will be administered TDS
Regulatory Status:	Unlicensed

Control Arm - Placebo

Brand name / Active ingredient:	N/A - placebo
Formulation:	Oral tablet to match active. Each tablet will be administered TDS
Regulatory Status:	Unlicensed

8.3 Manufacturing and Distribution

Packaging

Both the IMP and placebo treatments will be packaged in high density polyethylene (HDPE) bottles, sealed with child-resistant and tamper-evident caps. Participants will be supplied IMP/placebo in volumes as follows:

- For treatment days 1-14:2 x HDPE bottle containing 30 tablets
- For treatment days 15-168: 6 x HDPE bottle containing 105 tablets.

Tablets will be self-administered by participants and sufficient bottles will be dispensed at a visit (see 8.4) to continue treatment uninterrupted until next scheduled follow-up

Labelling

The IMP and placebo bottles will be labelled by the distributor(s) with Annex 13-compliant labels. Each bottle will be labelled and used for BASIS trial use only.

Shipment

The shipments will be temperature controlled via a GDP-approved courier service.

Regulatory Release to Site

This will be performed by the QP from Royal Free Specials Pharmaceuticals. A separate document will be generated to detail how the drug will be distributed.

Storage and Stability

The IMP should be stored between 15°C and 25°C and in its original packaging (to protect from light). Sites must monitor temperature and report any temperature deviations as outlined in the pharmacy manual.

8.4 Preparation, Dosage and Administration

Treatment should commence within 72 hours of randomisation.

8.4.1 Titration visits

Participants are to return at days 7 and 14 (+/- 1 day) for titration visits. Prior to the distribution of the appropriate IMP bottle, assessments must be completed as described in section 10.8.

The allocated treatment will be dispensed by the site pharmacist after receiving a study-specific prescription. The prescription will indicate that the trial participant is to be administered baclofen tablets or placebo as follows:

Week 0 (treatment days 1-7) – baclofen 10mg, or placebo, TDS
Week 1 (treatment days 8-14) – baclofen 10mg or 20mg, or placebo, TDS
Week 2 onwards (treatment day 15 onwards) – baclofen 10mg or 20mg or 30mg, or placebo, TDS

At visit weeks 1 and 2 the blinded prescriber will confirm that the participant is able to titrate up to the next dose level if this is in accordance with their randomised dose allocation. The unblinded pharmacist will then administer the appropriate dose in accordance with their allocation and titration stage:

Table 1: Dose titration and administered tablet strength by visit schedule

Daily dose/ Time	Visit 1 Week 0	Visit 2 Week 1	Visit 3 Week 2	Visit 4 Week 4	Visit 5 Week 8	Visit 6 Week 16	Visit 7 Week 24
30mg	10mg	10mg	10mg	10mg	10mg	10mg	End of treatment
60mg	10mg	20mg	20mg	20mg	20mg	20mg	
90mg	10mg	20mg	30mg	30mg	30mg	30mg	

Participants will be instructed to take one tablet orally three times per day and will be supplied with sufficient tablets to accommodate visit windows:

Table 2: Number of tablets prescribed by visit schedule

	Visit 1 Week 0	Visit 2 Week 1	Visit 3 Week 2	Visit 4 Week 4	Visit 5 Week 8	Visit 6 Week 16	Visit 7 Week 24
Bottle volume	30	30	105	105	105	105	End of treatment
Number of bottles administered	1	1	1	1	2	2	

8.5 Treatment Modifications

Each participant allocated to baclofen will start the trial at 10 mg TDS. Participants allocated to higher doses will be titrated upwards at a rate of 10 mg TDS each week until the assigned dose is reached. An upward titration has been shown to reduce the likelihood of adverse effects.

If the participant cannot tolerate the IMP and therefore the blinded prescriber decides that the participant cannot titrate up then the IMP will be discontinued.

8.5.1 Down titration at end of treatment (24 weeks)

When end of treatment is reached participants will be unblinded and a phased reduction in baclofen dose applied for those in the active arms.

The table below illustrates a down-titration regime; however, this can be adjusted for the individual needs of each participant. Down titration medication will be sourced via usual NHS supply arrangements.

Table 1. Down-titration regime:

Daily dose	Up to 72 hours (3 days) – post IMP discontinuation	4 - 6 days – post IMP discontinuation	7 - 9 days – post IMP discontinuation	10 - 12 days – post IMP discontinuation	13 days onwards post IMP discontinuation
30mg	5mg TDS	5mg BD	Not required	Not required	Not required
60mg	10mg TDS	5mg TDS	5mg BD	Not required	Not required
90mg	20mg TDS	10mg TDS	5mg TDS	5mg BD	Not required

8.5.2 Down titration if stopping treatment early

After a participant has entered the trial, the clinician is free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. However, the reason for doing so should be recorded. Given the double-blind design, it is not possible to know whether the participant is receiving the active product and at what dose, and therefore treatment modifications will not be possible without unblinding, at which point the participant will be unblinded, the randomised treatment/dose will cease and a phased reduction in baclofen dose may be applied as appropriate (see Table 1). The participant will remain within the trial for the purpose of follow-up and data analysis. If the participants have suicidal ideation or behaviour at follow up (e.g. score 3 and above on C-SSRS Screen) then the treatment should be discontinued and down-titration initiated.

8.6 Accountability Procedures

Drug accountability logs will be maintained by each site's pharmacy team throughout the trial; pharmacy will maintain an overall inventory of stock received, dispensed, returned, destroyed and quarantined.

If IMP stock received from the distributor is unexpected, wrong, damaged or not within expiry dates, the stock should be quarantined and LCTC contacted for further actions.

Drug bottles will be supplied with tear off labels that identify them as active/placebo and dose. The unblinded pharmacy staff will allocate appropriate bottles in accordance with randomised allocation and the titration stage. A record of individual prescriptions will be kept. There will be reconciliation between doses recorded as administered and doses returned. See the pharmacy manual for more details.

8.7 Assessment of Adherence

Adherence will be assessed using pill count.

All participants should be reminded and encouraged to properly adhere to the trial treatment at each study visit. There is no adherence cut-off for the BASIS trial.

8.8 Concomitant Medications/Treatments and Specific Restrictions

8.8.1 Medications/ Procedures Not Permitted

The following list of medications/treatments are not permitted as part of the BASIS trial:

- Trans-jugular intrahepatic porto-systemic shunt (TIPS) – if there is a need to insert TIPS for clinical reasons during the trial (as judged by the local PI), the participant will be removed from the trial. TIPS in situ at the time of recruitment is already an exclusion criterion.
- Development of CKD5 or requirement for haemodialysis
- Anti-craving pharmacotherapy (acamprosate, disulfiram naltrexone, nalmefene, baclofen) in previous 3 months
- Concurrent use of opioid substitution therapy

8.8.2 Data on Concomitant Medication

During each study visit data collection for concomitant medications will be limited to specific medications (see table 3).

Note that at the time of sample collection for PK/PD analyses data on all current concomitant medication will be collected.

Table 3: Concomitant drugs of interest

Drugs that may influence abstinence rates:
Already exclusion – i.e. licenced for alcohol use disorder
Naltrexone
Nalmafene
Acamprosate
Disulfiram
Drugs considered to have potential for abstinence treatment:
Gabapentin/Pregabalin
Topiramate
Prazosin / doxazosin
Varenicline
Ondansatron
Carbamazipine
Drugs that will be commonly used in this group of patients for liver disease
Carvidolol
Propanolol
Septrin
Rifaximin
Proton pump inhibiters – omeprazole / lansoprazole
Spironolactone
Frusemide
Thiamine / Vitamin B complex
Drugs that interact with baclofen
Tricyclic antidepressants
Lithium
Antihypertensives
Agents reducing renal function
Levodopa/dopa decarboxylase (DDC) inhibitor (Carbidopa)
Drugs causing Central Nervous System (CNS) depression

8.9 Medicinal products to be used with caution (30)

Levodopa/dopa decarboxylase (DDC) inhibitor (Carbidopa)

In patients with Parkinson's disease receiving treatment with baclofen and levodopa (alone or in combination with DDC inhibitor, carbidopa), there have been reports of mental confusion, hallucinations, nausea and agitation. Worsening of the symptoms of Parkinsonism has also been reported. Hence, caution should be exercised during concomitant administration of baclofen and levodopa/carbidopa.

Drugs causing Central Nervous System (CNS) depression

Increased sedation may occur when Baclofen is taken concomitantly with other drugs causing CNS depression including other muscle relaxants (such as tizanidine), with synthetic opiates or with alcohol (see section 4.7).

The risk of respiratory depression is also increased. In addition, hypotension has been reported with concomitant use of morphine and intrathecal baclofen. Careful monitoring of respiratory and cardiovascular functions is essential especially in patients with cardiopulmonary disease and respiratory muscle weakness.

Antidepressants

During concomitant treatment with tricyclic antidepressants, the effect of baclofen may be potentiated, resulting in pronounced muscular hypotonia.

Lithium

Concomitant use of oral baclofen and lithium resulted in aggravated hyperkinetic symptoms. Thus, caution should be exercised when baclofen is used concomitantly with lithium.

Antihypertensives

Since concomitant treatment with baclofen and anti-hypertensives is likely to increase the fall in blood pressure, the dosage of antihypertensive medication should be adjusted accordingly.

Agents reducing renal function

Drugs or medicinal products that can significantly affect renal function may reduce baclofen excretion leading to toxic effects

8.10 Overdose

Overdose where there is a need for urgent medical attention

Baclofen intoxication has been recognised for many years. The most frequent cause of baclofen toxicity is self-administered overdose. With the recent utilisation for AUDs the incidence of baclofen overdose has increased. It is noteworthy that baclofen overdoses have been recorded in patients prescribed a wide range of baclofen doses and not just the higher dose regimens.

Particular patient groups are potentially at increased risk of baclofen overdose and include: those with current suicide ideation, recent suicide attempt or coexistent substance abuse all of which are excluded from the trial.

After an acute ingestion of a large dose of baclofen central nervous complications include CNS depression ranging from drowsiness to coma. Seizures are prominent and will generally necessitate admission to a critical care facility and treatment is usual standard-of-care. In the setting of overdose, the half-life of baclofen may be as long as 36 hours post ingestion potentially necessitating a prolonged critical care stay.

Other observed complications of baclofen overdose include cardiac arrhythmias, in particular prolonged QT interval and heart block, requiring standard management in the appropriate clinical setting.

Any episode of significant baclofen self-poisoning necessitates admission to hospital for assessment and appropriate level of care. The patient information sheet and information to primary carers will stress this requirement.

Intentional or unintentional overdose

In circumstances of unintentional overdose, the participant will be continuing on IMP and it will be at the discretion of the local PI, after the discussion with the CI.

If the overdose was intentional the participant should be referred to appropriate psychiatric care as per usual care pathways.

Additional doses taken in error that requires medical intervention and/or in opinion of the local PI has been taken with an intent to self-harm should be reported as a Serious Adverse Event (section 12).

8.11 Unblinding

In the event of an emergency, a participant may be unblinded by the clinician at the recruiting site by contacting their local pharmacy department.

Clinicians carrying out emergency unblinding must be satisfied that it is a genuine emergency and that knowledge of the treatment allocation is needed to guide the appropriate clinical management of the participant.

The reason for unblinding must be recorded on the Unblinding CRF which should be provided (with all other CRFs completed up to the time of unblinding) to the LCTC as soon as possible.

Unblinding at trial completion for individual participants

At week 24 (i.e. completion of treatment for individual participants) or at withdrawal from trial treatment, if sooner, participants will be unblinded and returned to usual clinical care. The rationale for routine unblinding on stopping trial treatment is:

1. Where a participant meets the outcome for abstinence, withdrawal of the drug may pose a significant risk of relapse to drinking therefore participants may be offered the opportunity to continue baclofen treatment post trial end at the discretion of their treating clinician;
2. For those participants wishing to stop treatment appropriate down-titration of dose may be required to reduce possible adverse effects, and
3. Accurate information on dose and duration will be required for safe onward referral and return to usual clinical care.

Accidental Unblinding

All accidental unblinding must be documented appropriately according to LCTC processes. If accidental unblinding occurs at site, research staff at site should contact the Trial Manager as soon as possible. Where necessary, the TMG will review incident reports and determine if preventative actions are required.

9 OUTCOMES

Primary Outcome

Primary Objective	Primary Outcome Measures	Timepoint(s) of evaluation
The primary objective is to investigate the effect of baclofen compared with placebo in the treatment of AUD in patients with alcohol-related cirrhosis	Continued abstinence post randomisation for 24 weeks* measured using Timeline Followback	Baseline and weeks 4, 8, 16 and 24 *Note: Primary outcome is assessed at week 24*

*Participants who drink, but who do not meet the criteria for relapse, will be allowed to remain on trial treatment, if deemed safe by the local PI.

Secondary Outcome(s)

Objectives	Outcome Measures	Timepoint(s) of evaluation
Efficacy:		
To determine which dose(s) of baclofen is/are most effective in improving AUD treatment outcomes in patients with alcohol-related cirrhosis in comparison to placebo	Self-reported alcohol consumption since previous visit via Timeline Followback to measure: a) average units per drinking day b) percent days abstinent; c) number of heavy drinking days.	Baseline and weeks 4, 8, 16 and 24 of follow-up
	Changes in alcohol usage and dependency questionnaires (AUDIT, SADQ [if required at follow up], APQ).	Baseline and weeks 4, 8, 16 and24 of follow-up
	Quantity and Frequency of alcohol consumption measured using Timeline Followback .	Baseline and weeks 4, 8, 16 and 24 of follow-up
	Time to relapse (time to first alcoholic drink) measured using Timeline Followback .	Baseline and weeks 4, 8, 16 and 24 of follow-up
	Time to relapse (defined as time to consumption of ≥ 5 units for women, ≥ 6 units for men in a single day) measured using Timeline Followback .	Baseline and weeks 4, 8, 16 and 24 of follow-up
	Biological markers of alcohol consumption and liver function measured by: 1. Ethyl glucuronide (optional; measured in around 25% of participants) 2. Breath alcohol	Weeks 4, 8, 16 and 24 of follow-up, where optional consent has been provided Baseline, weeks 1, 2, 4, 8, 16 and 24 of follow-up

Objectives	Outcome Measures	Timepoint(s) of evaluation
	3. LFTs	Baseline, weeks 4, 8, 16 and 24 of follow-up
	Delta changes in liver function as per Child-Pugh and Model of End Stage Liver Disease (MELD-Na)	Baseline and weeks 4, 8, 16 and 24 of follow-up
	Alcohol craving by Penn Alcohol Craving Scale (PACS)	Baseline and weeks 4, 8, 16 and 24 of follow-up
	Subsequent hospital attendances and admissions (including unplanned use)	Weeks 4, 8, 16 and 24 of follow-up
	Rate of survival at time of data analysis using median duration of follow-up, assessed using ONS data	If required at final analysis
	Medication adherence	Pill count at: weeks 1, 2, 4, 8, 16 and 24 of follow-up
Assess the relationship between variability in baclofen exposure and efficacy and safety parameters.	Blood sampling to determine a population pharmacokinetic model for baclofen in patients with alcohol-related liver cirrhosis	Specific sampling approach across study visits at: weeks 4, 8, 16 and 24 of follow-up
Safety:		
To monitor and compare the safety profile of the baclofen arms, including dose dependency, in comparison to the placebo arm	Recording and assessment of related adverse events	Weeks 1, 2, 4, 8, 16 and 24 of follow-up

10 PARTICIPANT TIMELINES AND ASSESSMENTS

10.1 Participant Identification and Screening

Individuals who are potentially appropriate for trial recruitment will be identified by a person responsible for the clinical management of the patient prior to a formal eligibility screen by a member of the research team.

The sources of these patients may be via e.g. admission to a secondary care setting under the care of a Hepatologist during a hospital spell in relation to their underlying liver disease or via assessment by the Alcohol Care Team contemporaneously managing the participants.

All measures to assess eligibility form part of routine clinical care, except pregnancy screening in women of childbearing potential* as defined as per Clinical Trial Facilitation Group (CTFG) guidance (36).

*fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high folic/le stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required,

In these women, informed consent will be required prior to undertaking a pregnancy test as part of eligibility screening.

An anonymised screening log of patients who are assessed for eligibility but not randomised will be maintained as this will provide important information for monitoring purposes.

10.2 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Written informed consent is required for all patients participating in LCTC coordinated trials. The process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered. In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to the principles of GCP and to the ethical principles that have their origin in the Declaration of Helsinki (1996). Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent, they do not have to give a reason.

Prospective Informed Consent Process

Patients will be approached by a member of the local research team.

A written information sheet that forms part of the ethically approved Information Sheet and Consent form will be provided. This includes a detailed explanation of the study and makes clear that the rights and welfare of the participants will be protected; it will be emphasised that consent may be declined or withdrawn at any time in the future without the quality of care being adversely affected. The research staff

will facilitate verbal discussions about the research and the consent process, as well as providing answers to any questions that arise.

After verbal and written information has been provided, the individual seeking consent will ensure that the potential participant has fully understood all the information and will ask if they are happy to consent to participation in the trial. Where this is the case, written informed consent will be obtained by means of a dated patient's signature on the consent form. This should be countersigned and dated by the person who obtained informed consent i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility. If the participant is unable to read/write, then an impartial witness will be present during the informed consent process and must append his/her signatures to the consent form.

- The original signed document will be retained in the trial site's Investigator Site File (ISF) and copies will be made:
- One copy provided to the patient for their information
- One copy transferred to the LCTC
- One copy filed in the participant's medical records paper/electronic.

N.B. Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records.

Loss / Regain of capacity

If the participant who has consented and loses capacity, their previously provided consent remains valid. They will be monitored for any signs of objection or distress during trial specific procedures that would prompt a reconsideration of their continued participation. This would also be the case if their nominated relative raised concerns regarding their continued participation. If a participant loses and regains capacity, their continuing consent will be reaffirmed.

Consent for pregnancy test

Pregnancy is an exclusion criterion and therefore women of childbearing potential require a negative pregnancy test in order to be eligible. As this is not part of routine care, written Informed consent must be obtained prior to the pregnancy test being undertaken. Potential participants must be made aware that they are under no obligation to take part on the trial if the test is negative. Women with child bearing potential must consent to highly effective contraception* defined as per CTFG guidance (36), as below:

- Oral, intravaginal or transdermal combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner (a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success
- sexual abstinence (considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject)

Women who are found to be pregnant without prior knowledge will be given appropriate support and this information will be passed to the clinician responsible for their care.

10.3 Eligibility Assessment and Confirmation

Eligibility confirmation is required at registration for the two-week run-in and at randomisation. Eligibility can only be confirmed by an appropriately qualified medical professional who is named on the delegation log and must not occur until informed consent is documented. Eligibility criteria are described in detail in Section 7.

Eligibility confirmation must be documented in the participant's medical notes and then on the trial's Eligibility eCRF. Details must include at a minimum who confirmed full eligibility, when this was confirmed, and when the participant was formally entered into the trial (randomised).

10.4 Week -2 to Week 0

10.4.1 Registration Assessments

Registration procedures should be completed as per the Schedule of Assessments and Follow-Up (Section 10.7) in order to accurately complete the Registration eCRF and collect the necessary information for the trial analyses. This includes the collection of the following:

- Routine information e.g. medical history /concomitant medication / vital signs / relevant blood test results etc. This information can be transcribed from the patient's medical notes into the eCRF once appropriate consent has been obtained.
- Demographic information (age, sex, year of birth, ethnicity)
- Completed Timeline Follow Back

The patient can proceed to run-in once all the registration procedures have been completed.

10.4.2 Two Week Run-in

Following registration all participants will receive care as usual and will be invited to attend a randomisation visit. There will be a 2-week run-in period between the registration and the randomisation visits, during which participants will be required to abstain from alcohol.

All participants will undergo screening to detect suicidal ideation using the C-SSRS Screen between day 7 and day 10 post registration. This will ensure time for patients to receive appropriate medical treatment and reduce test anxiety.

A score of 3 or more will result in referral for mental health assessment following local standard of care procedures.

At the randomisation visit, results of mental health assessment will determine eligibility (i.e. patient determined to be at risk of suicide will not be eligible for the trial).

After two weeks, all participants will be assessed for entry to randomisation (section 10.5). Participants who do not meet the entry criteria will not be randomised.

10.5 Week 0

10.5.1 Baseline Assessments - Randomisation

Baseline assessments should be completed as per the Schedule of Assessments (Section 10.7) in order to accurately complete the Baseline eCRF and collect the necessary information for the trial analyses. This includes the following assessments: Audit, SADQ, PACS, APQ, Timeline Followback, Breath Alcohol test, Pregnancy test, record of Childs Pugh Categorisation, Assessment of Adverse Events and MELD/Na.

Routinely collected information, e.g. medical history / concomitant medications / vital signs / relevant blood test results etc. can be transcribed from the patient's medical notes into the eCRF.

The patient can proceed to randomisation once all the baseline assessments have been completed.

These aspects of the trial should happen concurrently. Participants will then be randomised as per section 10.5.2. Participants who do not meet the eligibility criteria will not be randomised.

10.5.2 Randomisation Process

Participants will be randomised via a secure (24-hour) web-based randomisation system controlled centrally by the LCTC to receive either one of the four study arms (in a ratio of 1:1:1:1). Participants will be stratified by recruitment site and Child-Pugh classification.

Randomisation should occur no more than 2 days after the completion of the week 0 assessments.

A personal login username and password, provided by the LCTC will be required to access the randomisation system. Designated research staff will be issued with their personal login and password upon completion of training in the use of the system. This training will be coordinated by the LCTC.

When the system requirements (e.g. confirmation of valid consent and meeting eligibility etc) are confirmed, the participant's unique study number (randomisation number) will be displayed on a secure webpage. An automated email confirmation, without any details of treatment allocation, will be sent to the authorised randomiser, Principal Investigator (PI) and Trial Manager.

An additional email will be sent to the designated pharmacy contact/s to confirm randomisation number and treatment allocation. It is the responsibility of the PI or delegated research staff to inform the pharmacy department at their site of impending randomisation to ensure there is sufficient supply of the study treatments.

Randomisation: web access http://www.basis-study.com

If there are any problems with the randomisation systems contact the LCTC on 0151 794 0249 or via email on basis@liverpool.ac.uk

(Note: the LCTC is open from 0900 – 1700, Monday – Friday, excluding public holidays)

Following randomisation, participants should receive their randomised treatment allocation as described in Section 8.4.

Randomisation System Failure

In the event of a randomisation system failure, the centre should contact the coordinating team at the LCTC (Monday to Friday between 9:00 to 17:00 excluding bank holidays and University closure days) to try to resolve the problem. If the problem cannot be resolved the coordinating LCTC will perform central randomisation and randomise the participant using the back-up randomisation system. The back-up randomisation system is an exact replica of the live system but is based on a standalone PC at LCTC.

10.6 Treatment

Participants will be administered their allocated treatment within the time window specified in section 8. Unblinding procedures and processes are detailed in Section 8.11.

10.7 Schedule for Assessments and Follow-up

All assessments and follow up are to be conducted in line with the Schedule of Assessments below:

Time	Week -2	Week -2 to Week 0	Week 0*	Week 1	Week 2	Week 4	Week 8	Week 16	Week 24		At final analysis
Procedures	Registration	Run-in	Baseline & Randomisation	Follow-up & Titration 1	Follow-up & Titration 2	Follow-up visit	Follow-up visit	Follow-up visit	Study Completion	Premature Discontinuation	
Signed Informed Consent	X										
Pregnancy test (women of child bearing potential)			X								
Medical Confirmation that Eligibility Criteria are Fulfilled	X		X								
Review of Medical History	X		X								
Collection of Demographics	X										
Vital signs	X		X	X	X	X	X	X	X	X	
Review Concomitant Medications	X		X	X	X	X	X	X	X	X	
Run-in		X									
Randomisation			X								
Study Intervention (IMP distribution)			X	X	X	X	X	X			
Timeline Followback	X		X			X	X	X	X		
Columbia Suicide Severity Risk Scale Screen (C-SSRS Screen)		X		X	X	X	X	X	X		
Mental Health Assessment for C-SSRS scores of 3 or above		X		X	X	X	X	X	X		
Alcohol questionnaires (Audit, , PACS, APQ)			X			X	X	X	X		
Alcohol questionnaire SADQ			X			X**	X**	X**	X**		
Breath Alcohol Test			X	X	X	X	X	X	X		
Blood sample (PK-PD) 250 patients (n =1000 samples)						X	X	X	X		
Childs Pugh Categorisation^			X			X	X	X	X	X	
Model for End Stage Liver Disease (MELD-Na)			X			X	X	X	X	X	
Assessment of Adverse Events			X	X	X	X	X	X	X	X	
Adherence (Pill count)				X	X	X	X	X	X	X	
Blood samples - LFT, U+E Clotting profile/INR and full blood count	X		X			X	X	X	X	X	
Urine for Ethyl glucuronide 100 consecutive patients (total n=400 samples)						X	X	X	X		
Hospital attendances and admissions data collection						X	X	X	X		
Handover to routine care									X	X	
ONS extract – mortality data (if required) collected via NHS England/ PBPP-HCP											X

*At Week 0, all procedures should be done before randomisation and administration of first treatment bottle.
** Only completed if the participant has started to drink alcohol as confirmed by the TLFB.

^ Requires assessment of Total bilirubin, µmol/l (mg/dl); Serum albumin, g/l; Prothrombin time, prolongation (secs); Ascites; Hepatic encephalopathy.

All Assessments should be conducted by an individual who is appropriately trained and competent of trial procedures.

10.8 Follow-up Visits (Titration Visits, Weeks 1 and 2)

The 24-week follow-up period will begin at the time of randomisation, if different to date of randomisation. Participants are to return at days 7 and 14 (+/- 1 day) for titration visits. Prior to the distribution of the appropriate IMP bottle, the following procedures need to be undertaken:

1. Assessment of Adverse Events;
2. Adherence measurements (pill count)
3. Review of medications for contraindicated treatments;
4. Breath alcohol test
5. Vital signs
6. C-SSRS Screen and onward referral to mental health practitioner if scored 3 and above

10.9 Follow-up Visits (Weeks 4, 8, 16 & 24)

These visits should occur within +/- 4 days of the specific scheduled date.

Participants will be invited to research visits at week 4, 8, 16 and 24. During these visits baseline measures will be repeated, except for demographics, and participants will be assessed for outcomes according to the measurements outlined below. Data will also be extracted on hospital attendances and admissions during the follow-up period.

If a participant attends their follow-up appointment and in the opinion of the research team is intoxicated or showing signs of suicide ideation or behaviour, they will be unblinded, appropriate titration of treatment will be initiated. Follow-up data will continue to be collected.

10.9.1 Efficacy Assessments

10.9.1.1 Participant Reported Outcomes of Alcohol use – Baseline, Week 0, Follow-up weeks 4, 8, 16 & 24

- Alcohol Timeline Followback [37] - A drinking assessment method that obtains estimates of daily drinking that will be used to assess the primary outcome. The method has been evaluated in both clinical and non-clinical settings. The tool can generate variables that provide a wide range of information about an individual's drinking (e.g., quantity, frequency, and variability).
- Columbia-Suicide Severity Risk Scale Screen (C-SSRS Screen) [38] – The C-SSRS screen version has been validated as a screening tool for suicide risk with a high NPV and adjusted odds ratio for future suicide. The Screen is feasible to use in acute settings as an initial step before a comprehensive clinical assessment of suicide risk. C-SSRS is endorsed by FDA for clinical trials, and has been recommended for this trial by MHRA. Alcohol use disorder identification test (AUDIT) [39] – A tool developed by the World Health Organisation to screen for excessive drinking and determining level of risk.
- Severity of Alcohol Dependence Questionnaire (SADQ) [40] - A tool developed by the World Health Organisation to evaluate the extent to which an individual is dependent on alcohol use. This tool will only be completed at baseline and then will only be required at follow up if a participant has started to drink alcohol.
- The Alcohol Problems Questionnaire (APQ) [41] – An instrument for measuring alcohol-related problems that consists of 44 items divided into five subscales measuring the perceived costs of drinking in terms of financial, legal, physical, social, and psychological domains.

- Breath alcohol – Measure to be used to confirm current alcohol intoxication status. Each site will be provided with a calibrated breathalyser.
- Urinary ethyl glucuronide (if consented). - Ethyl glucuronide can be detected in urine for up to 80 h after ethanol consumption and thus provides an objective biomarker for recent alcohol consumption. Ethyl glucuronide will be assessed using a sensitive and specific assay which will be developed at the University of Liverpool

10.9.1.2 Participant Reported Outcomes Alcohol Craving – Baseline, Week 0, Follow-up weeks 4, 8, 16 & 24

- The Penn Alcohol Craving Scale (PACS) [42] - A 5-item questionnaire that measures an individual's craving to drink alcohol in the past week.

10.9.1.3 Clinical Measures of Liver function – Baseline, Week 0, Follow-up weeks 4, 8, 16 & 24

- Severity of cirrhosis will be defined by validated scoring models (Child-Pugh/ Model for End-Stage Liver Disease [MELD-Na]) (see Table 1 for Child Pugh calculation and the calculation for model for end-stage liver disease below). Scores for both models will be collected at each research time point to monitor changes in disease severity.

Table 1: Child Pugh Score

Measure	***1 point***	***2 points***	***3 points***
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-51 (2-3)	>51 (>3)
Serum albumin, g/l	>35	28-35	<28
international normalised ratio (INR	<1.7	1.7- 2.3	>2.3
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Each measure is scored 1-3, with 3 indicating most severe derangement

Interpretation: Class A: 5-6. Class B: 7-9. Class C: 10-15.

Model For End-Stage Liver Disease (MeId)-Na

MELD-Na=MELD + 1.32 x (137 - Na) - [0.033 x MELD*(137 - Na)]

To calculate a MELD-Na score biochemical results for contemporaneous levels of
Serum Creatinine (mg/dl), Bilirubin (mg/dl), INR are required.

- Liver function tests – Routine measure in the management of patients with liver disease that will enable the validated liver prognostic scores to be calculated.

- Full blood count – Standard of care for the secondary care management of patients with liver disease

- Clotting screen – INR is SOC for the management of patients with liver disease and an essential component of clinical prognostic tools

10.9.2 Urinary ethyl glucuronide (urine) sampling

Participant selection

A maximum of 100 consecutive participants will be invited to consent to provide four samples throughout their participation in the study. Participants will be asked to donate a 60ml sample of urine at each appropriate visit.

The LCTC will inform the sites when the recruitment for this part of the study is completed.

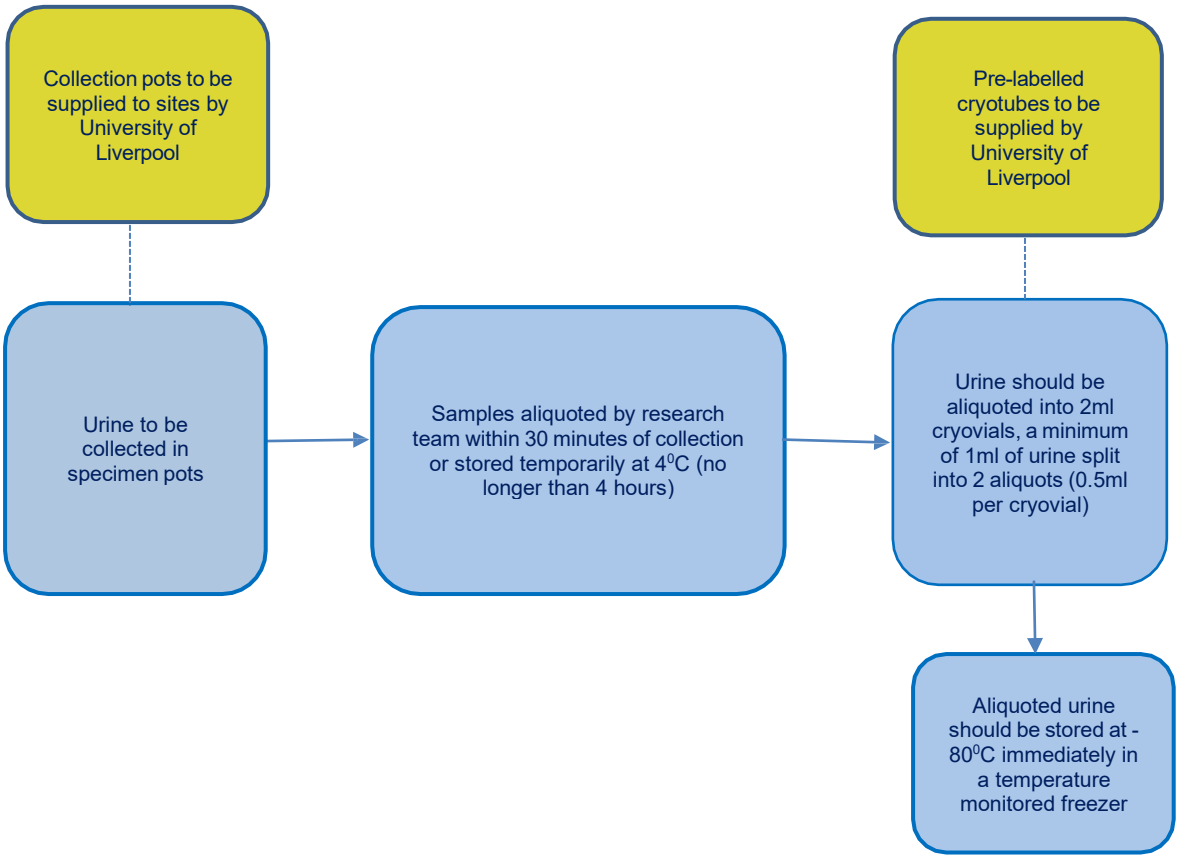
Urinary ethyl glucuronide sampling

Ethyl glucuronide can be detected in urine for up to 80 hours after ethanol consumption and thus provides an objective biomarker for recent alcohol consumption. This will be used to validate self-report alcohol measures for all the participants.

The urine samples will be collected in larger specimen containers approx. 60ml, which will be aliquoted into 2ml cryovials by a member of the site team This has to be done within 30 minutes of collection or temporarily stored at 4°C for no longer than 4 hours. A minimum of 1ml of urine split into 2 aliquots (0.5ml per cryovial). Urine should be stored at -80°C in a temperature monitored freezer until the collection (See Figure 1).

Batches of samples from sites will be transferred to the Department of Antimicrobial Pharmacodynamics and Therapeutics (APT) at the University of Liverpool (GCP compliant laboratory) by arranged courier service at the end of the trial. All relevant samples will be transferred on dry ice in appropriate packaging in solid carbon dioxide. The University of Liverpool will be custodian of the samples, which will be retained until they expire.

Figure 1. Urine sample collection flowchart:



10.9.3 Safety Assessments

Side effects – To be assessed based on the onset of new symptoms since treatment initiation. All symptoms are to be recorded in the appropriate section of the eCRF in accordance with section 12.

Drug adherence – Pill count .

10.10 Intervention Discontinuation and Participant Discontinuation/Withdrawal

In consenting to the trial, participants agree to all trial activities including administration of the trial intervention, follow-up assessments / visits and data collection/ optional blood and urine sample collection. Every effort should be made to facilitate the completion of these. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

10.10.1 Premature Discontinuation of Trial Intervention

Participants may discontinue treatment for reasons including, but not limited to:

- Participant-led i.e. request by the participant / person with parental responsibility / legal representative / consultee
- Unacceptable toxicity (see Section 12 for Adverse Event reporting)
- Intercurrent illness preventing further treatment.
- Overdose
- Pregnancy
- Death
- Suicide ideation or behaviour
- Clinician-led:
    - Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion.
    - Reasons of non-adherence or non-compliance with treatment or other trial procedures
    - Participant meets an exclusion criterion (either newly developed or not previously recognised)

Discontinuation from trial does not mean discontinuation of the study altogether, and the remaining study procedures, follow up assessment / visits and data collection should be completed as indicated in the protocol (unless consent is specifically withdrawn). Data to be collected at the time of discontinuation is identical to that outlined in follow-up visits (please see Week 4 in section 10.7 as guide to data collection in this circumstance).

10.10.2 Participant Withdrawal from Follow Up

Participants are free to withdraw from follow up at any time without providing a reason, though a reason should be recorded if one is given. Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses. The participant will not contribute further data to the study and the LCTC should be informed via email to the LCTC (basis@liverpool.ac.uk) and via completion of a Withdrawal eCRF to be returned to the LCTC within 7 days.

If the participant expresses a wish to withdraw from follow up, the research team at site should ascertain if this is for all elements of trial follow-up, or if for example data from routine assessments can still be

collected for the trial. In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable. Any SAEs will be notifiable to the LCTC via processes detailed in Section 12 even if a participant has withdrawn from follow up.

10.10.3 Participant Transfer

If a participant moves from the area, every effort should be made for the participant to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the participant or for follow-up via GP. The new site will be given access to the participants in the database. – The participant remains the responsibility of the original site until the new site PI has completed the Transfer eCRF.

If the participant moves from the area and no participating centre is within an appropriate distance, the participant will be considered lost to follow-up, although appropriate arrangements should be made for unblinding and down-titration of trial treatment, where applicable (section 8.5), prior to discontinuation and transfer. Additionally, suitable active monitoring of the participant for AE and SAE should occur until 7 days post discontinuation of the trial treatment.

10.10.4 Loss to Follow-up

A participant will be considered lost to follow up if s/he fails to return for any scheduled visits and is not contactable by the site research team.

If a participant fails to attend/facilitate a required study visit the following actions must be taken:

- Site will attempt to contact the participant and reschedule the missed visit within four days of the scheduled visit and advise the participant on the importance of maintaining the assigned visit schedule.
- Before a participant is deemed to be lost to follow up, site research staff will make every effort to regain contact with the participant (i.e. three telephone calls and, if necessary, a headed letter to last known address). These efforts should be recorded in the patient medical notes.
- Contact will be attempted three times via the back-up contact (nominated contact if provided at registration)

  If the participant continues to be unreachable, they should be considered withdrawn from the study with a primary reason of lost to follow up and this should be recorded on the appropriate CRF.

10.11 End of Trial

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. The trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC).

Site and closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC and MHRA within regulatory timelines.
- Trial-related materials reconciled and returned/disposed of as appropriate see section 8.6 for IMP.
- All site data entered onto the study database, discrepancies raised and satisfactory responses received.
- Quality Control checks of the Investigator Site Files, Pharmacy Files and Trial Master File as appropriate.

10.11.1 Study Discontinuation

If the trial is discontinued, all participants already randomised will be unblinded and returned to usual clinical care with appropriate instruction for downward titration for those receiving baclofen (section 8.5). Active monitoring for adverse events will be maintained for 7 days post last dose of trial treatment. The decision to continue using baclofen outside of the trial is a decision to be made by the patient and his/her medical team.

11 PK/PD SUB-STUDY

11.1 Objective

Develop a population pharmacokinetic model for baclofen in patients with alcohol-related liver cirrhosis

11.2 Overview

To quantify and understand the variability in baclofen concentrations at different doses, and the relationship to PD parameters, a PK/PD sub-study will be conducted in accordance with FDA Guidance (July 2019). Blood samples will be obtained at different time points after drug intake (dose escalation or follow-up visits). In some patients, (initially Liverpool only), multiple samples will be obtained on the same study visit, while in others multiple samples will be taken on different days.

Overall, we will collect approx. 1000 blood samples from consented participants – this will provide good precision to estimate both within and between participant variability.

Scheduling of sampling for an individual participant will be provided at randomisation and across the cohort will ensure a range of samples encompassing pre-dose samples, and with exact timings of dose administration and sample times recorded.

Exposure data on baclofen (dose, time of dose, adherence, etc.) will be used to construct a population PK model, with PD parameters including lapse and PACS. Drug concentrations in plasma will be measured using a validated, sensitive and specific assay which will be developed at the University of Liverpool using liquid chromatography-mass spectrometry (LC-MS). This will be done under GCLP (good clinical laboratory practice) conditions.

Methods

Two distinct studies will be undertaken:

1. **Pharmacokinetic Rich sampling**
2. **Pharmacokinetic/ Pharmacodynamic Sparse sampling**

11.3 Pharmacokinetic Rich Sampling

Participant selection

It is intended that 24 BASIS participants will be recruited into the rich sampling sub study. Participants will primarily be recruited from the BASIS participants at the Royal Liverpool Hospital site, which may be extended to other sites if recruitment target indicates a need.

All potential participants will be given the patient information leaflet and consent form. If the individual agrees to participate in the study, and provides written informed consent, they will be entered into the sub study on day 1.

Participants will be requested to fast from midnight prior to administration of the investigational active compound/placebo. Pharmacokinetic blood samples will be collected by an intravenous cannula or

venepuncture at regular intervals over the next 24 hours. The participant will take the next dose of the IMP 24 hours later after the last PK blood sample is taken as per their randomisation schedule.

Sampling – Rich blood samples

Prior to each sample being taken from the cannula 0.5mls of blood will be drawn and discarded. The cannula will be flushed with 2mls of 0.9% saline each time a sample is taken. At each designated time point 4.9 ml of blood will be taken into lithium heparin tubes. Blood samples will be centrifuged at 1500 g within 30 minutes of collection or stored at 4 °C before centrifugation (see Figure 2).

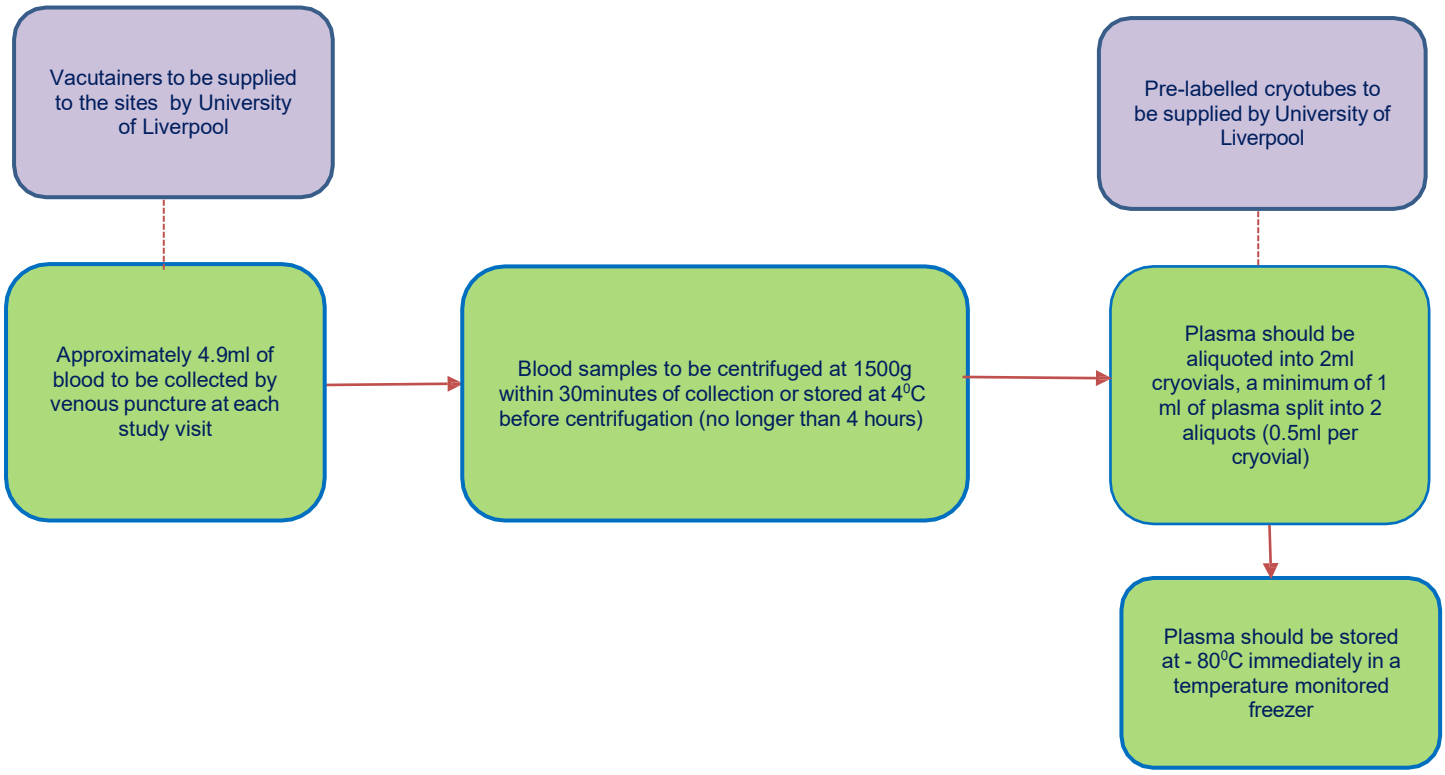
Blood plasma will be aliquoted by a member of the research team into 2 ml cryovials. A minimum of 1ml plasma to split into 2 aliquots (0.5 ml per cryovial). Plasma will be stored at -80oC until they are transferred to the Department of Antimicrobial Pharmacodynamics Pharmacology and Therapeutics (APT) labs.

All relevant samples will be transferred on dry ice in appropriate packaging in solid carbon dioxide to the Department of Antimicrobial Pharmacodynamics Pharmacology and Therapeutics (APT) at the University of Liverpool. The University of Liverpool will be custodian of the samples, which will be retained until they expire.

PK Blood Sampling Schedule:

Blood Sampling	Blood sampling times post dose administration (all times +/- 10%)
Day 1 Blood sampling from cannula into 1 x 4.9ml Li Heparin tube	• 0 minutes (pre-dose administration) • 15 minutes (+/- 1.5 min) • 30 minutes (+/- 3mins) • 1 hour (+/- 6mins) • 2 hours (+/- 12mins) • 4 hours (+/- 24mins) • 6 hours (+/- 36mins) • 8 hours (+/- 48mins) • 12 hours (+/- 72mins/ 1hr 12mins)
Day 2 (12-hours later) Blood sampling from cannula into 1x 4.9ml Li Heparin tube (prior to next dose of IMP)	• 24 hours (+/- 144min/ 2hrs 24mins)

Figure 2. Plasma sample collection flowchart:



11.4 Pharmacokinetic/ Pharmacodynamic sparse sampling

11.4.1 Blood sampling

Participant selection

Overall, we will collect 1000 blood samples from at least 250 consented participants who will agree to provide a total of four blood samples throughout their participation in the study.

For each blood sample, it will be important to record both the time the last dose of the IMP was taken and the time of the blood sample.

The LCTC will inform the sites when the recruitment for this part of the study is completed.

Blood Sampling (sparse)

Prior to each sample being taken from the cannula 0.5mls of blood will be drawn and discarded. The cannula will be flushed with 2mls of 0.9% saline each time a sample is taken.

At each designated study visit 4.9 ml of blood will be taken into lithium heparin tubes. Blood samples will be centrifuged at 1500 g within 30 minutes of collection or stored at 4 °C before centrifugation.

Blood plasma will be aliquoted by a member of the research team into 2 ml cryovials. A minimum of 1ml plasma to split into 2 aliquots (0.5 ml per cryovial). Plasma will be stored at -80ºC until the end of the trial (see Figure 2).

All relevant samples will be transferred in appropriate packaging in solid carbon dioxide to the Department of Department of Antimicrobial Pharmacodynamics and Therapeutics (APT) at the University of Liverpool. The University of Liverpool will be custodian of the samples, which will be retained until they expire.

11.5 Data collection

A sub study eCRF will need to be completed alongside each blood donation.

11.6 Analysis plan

A population PK model will be fitted to the sparse PK data collected from each patient. The different dosage levels provide an opportunity to test for linearity. Clinically relevant covariates will be examined and incorporated into the final model as appropriate. Bayesian estimates of each patient's PK will be used to determine measures of drug exposure experienced by each patient (e.g. area under the concentration time curve; AUC) and these measures will be linked to pharmacodynamic/clinical endpoints using logistic regression. If drug exposure is an important determinant of clinical response, then an AUC value that separates the study population into a high and low probability of a clinical response will be apparent. A series of Monte Carlo simulations will be performed to identify the regimen of baclofen that results in the attainment of the target AUC value for a suitably high proportion of the simulated population (e.g. >90%).

12 SAFETY REPORTING

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to LCTC . This includes SAEs related to IMPs. Any trial specific SAE reporting exceptions are detailed in section 12.8.

12.1 Terms and Definitions

Adverse Event (AE)
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.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Reaction (AR)
Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Serious Adverse Event (SAE)
Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Serious Adverse Reaction (SAR)
An adverse reaction which meets the definition of serious (see Section 12.2) is a Serious Adverse Reaction. A Serious Adverse Reaction event that has been assessed as ‘expected’ (see Section 12.5) according to the RSI(see below) will remain classified as a Serious Adverse Reaction only, however Serious Adverse Reactions that are considered ‘unexpected’ will be further classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see below).

Suspected Unexpected Serious Adverse Reaction (SUSAR)
An adverse reaction that is classed in nature as serious and “unexpected” (i.e. not listed within the RSI approved for the trial by the MHRA and current at the time of onset of the SUSAR).

Reference Safety Information (RSI)
The information used for assessing whether an adverse reaction is expected (see section 12.6). This is contained in the Summary of Product Characteristics (SmPC) for the product is approved for use by the MHRA. The RSI for this trial is defined in section 12.6.

12.2 Assessment of Seriousness

The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

A safety event / reaction is assessed as serious if it:

- Results in death;
- Is life threatening (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death);
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE);
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
- Consists of a congenital anomaly or birth defect (in offspring of subjects, or their partners, taking the IMP regardless of time of diagnosis);
- Other important medical events (these may not result in death, be life-threatening, overdose, secondary malignancy or require hospitalisation, but may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

[#]safety event / reaction applies apply to either AEs, or ARs, or Related AEs.

12.3 Severity of Adverse Events

All adverse events should be assessed for severity. The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions in the table below:

Table 1: Severity Grading

Severity	Description
Mild	Does not interfere with routine activities.
Moderate	Interferes with routine activities.
Severe	Impossible to perform routine activities.

N.B. A distinction is drawn between **serious** and **severe** AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in Section 12.2. Hence, a severe safety event need not necessarily be a "serious" safety event.

12.4 Assessment of "Causality" - Relationship to Trial Treatment

Safety events must be assessed to determine whether they are related to the trial IMP(assessment of causality). The assessment of causality must be made by the investigator responsible for the care of the participant using the definition in the table below. Assessment should be made against the IMPs administered to the participant. Whilst the Sponsor/CI/delegate may also provide an assessment of causality for a safety event, the opinion of the site must NEVER be downgraded. In the case of differing opinion, the event will be treated as related, but both opinions should be provided when reporting to ethics/regulators.

The assignment of the causality should be made using the definitions in the table below:

Table 2: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Events that are assessed as being possibly, probably or almost certainly related will be reported as having a reasonable possibility of being related, and events assessed as unrelated or unlikely will be reported as having no reasonable possibility of being related.

Assessment of causality should be made based on the SmPC and known risk profiles of other drugs in the same class. If any doubt about the causality exists, the local investigator should inform the LCTC who will notify the Chief Investigator. In the case of discrepant views on causality between the treating investigator and others, the opinion of the treating investigator will never be downgraded and the MHRA & REC will be informed of both points of view.

12.5 Assessment of "Expectedness"

There is no requirement for a reporting investigator to assess expectedness. Assessments of expectedness are sponsor's responsibility and are delegated to the LCTC and Medical Reviewer. Assessment of "expectedness" will be performed by the Chief Investigator or other medically qualified collaborator as delegated by the Sponsor.

An event will be considered unexpected if it is not listed within the current and approved RSI (see section 12.6) for the study at the time of the event's onset. The nature, severity, or frequency of the event should be considered – if this is not consistent with that described for the type of event in the RSI the event should be assessed as unexpected.

12.6 Reference Safety Information

The Reference Safety Information (RSI) for BASIS is Section 4.8 of the Summary of Product Characteristics (SmPC) for Baclofen Tablets BP10mg provided by Accord UK Ltd.

12.7 Time Period for Active Monitoring of Safety Events

IMPORTANT: Any serious adverse events occurring in the trial participants after the end of the below described "active monitoring" period which meet the definition of serious (see section 12.2) and are recorded for this study must continue to be reported by sites to the Sponsor and LCTC if the PI becomes aware of them. Reporting should be in accordance with the timeframes and procedures described in section 12.11. The same processes established for SAEs within the active monitoring period should be followed for these events.

Active monitoring of safety events experienced by trial participants will be from the period of registration and continue until 7 days from the last administration of the trial treatment dose.

Pregnant women will be followed up until at least the outcome of the birth (see Section 12.9 for more information on reporting pregnancy).

12.8 Notes on Safety Event Recording

The following events must be recorded for the purposes of the trial:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents
- Pregnancy (See section 12.9 for more details)

Do not record[1]:

- Medical or surgical procedures - the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery[1]
- Unintentional overdose of medication **without signs or symptoms***[2]
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

[1] Cosmetic elective surgery is cited here as example of an event that is not reportable as an AE, however such an occurrence may need to be reported elsewhere in the eCRF if it is deemed a secondary consequence of the IMP (e.g. fall from baclofen-related sedation).
[2] Note that intentional overdose of medication with or without signs or symptoms must be reported as an AE. Unintentional overdose may still require investigation to ensure other protocol and regulatory requirements are met e.g. for IMP management and administration, or to ensure participant safety. If applicable, refer to appropriate part of Treatment section 8.10 (Overdose).

The events above do not need recording as the trial is considered low-risk given previous experience of baclofen in patients with alcohol-related cirrhosis by members of the research team and from evidence of published studies.

*N.B. If overdose occurred **with** resulting signs and symptoms that meet the protocol criteria for AE/AR/SAE/SAR/SUSAR then they should be reported accordingly (see section 12 for more information) and the overdose highlighted to the LCTC team.

12.9 Reporting of Pregnancy

Historically due to the hormonal and metabolic disturbances observed in cirrhosis there is a reduction in female fertility due to anovulation. However, advances in clinical hepatology and maternal care has led to increasing pregnancies in women with cirrhosis. Major concerns in this patient group of becoming pregnant are the risk of variceal bleeding which occurs in 30-50% of woman because alcohol consumption increases intrahepatic resistance and as such the risk of variceal bleeding.

Baclofen crosses the placenta and has been shown to increase birth defects when compared to controls. Given this data, women of childbearing potential will have a pregnancy test during screening and excluded if it is positive. Assurances will be sought that effective contraception will be utilised during their participation in BASIS defined as per CTFG guidance.

If pregnancy occurs during the intervention period of the trial, this must be notified to the LCTC using the appropriate eCRF within 24 hours of the research team becoming aware. Women who become pregnant whilst participating in the study should discontinue trial treatment, be unblinded and down-titrated as per section 8.5 if on active baclofen.

The decision on whether to initiate/re-initiate baclofen therapy outside of the trial will be at the discretion of the responsible clinician. The pregnancy must be followed up by the site research team until at least the outcome of the birth, which should be reported to LCTC.

Any pregnancies which result in a safety event assessed as “serious” (e.g. birth defect) must also be reported separately on the appropriate Safety Event eCRFs in accordance with processes described in section 12.11. All pregnancies and outcomes reported to LCTC will be notified to the study Sponsor and monitored by trial oversight committees.

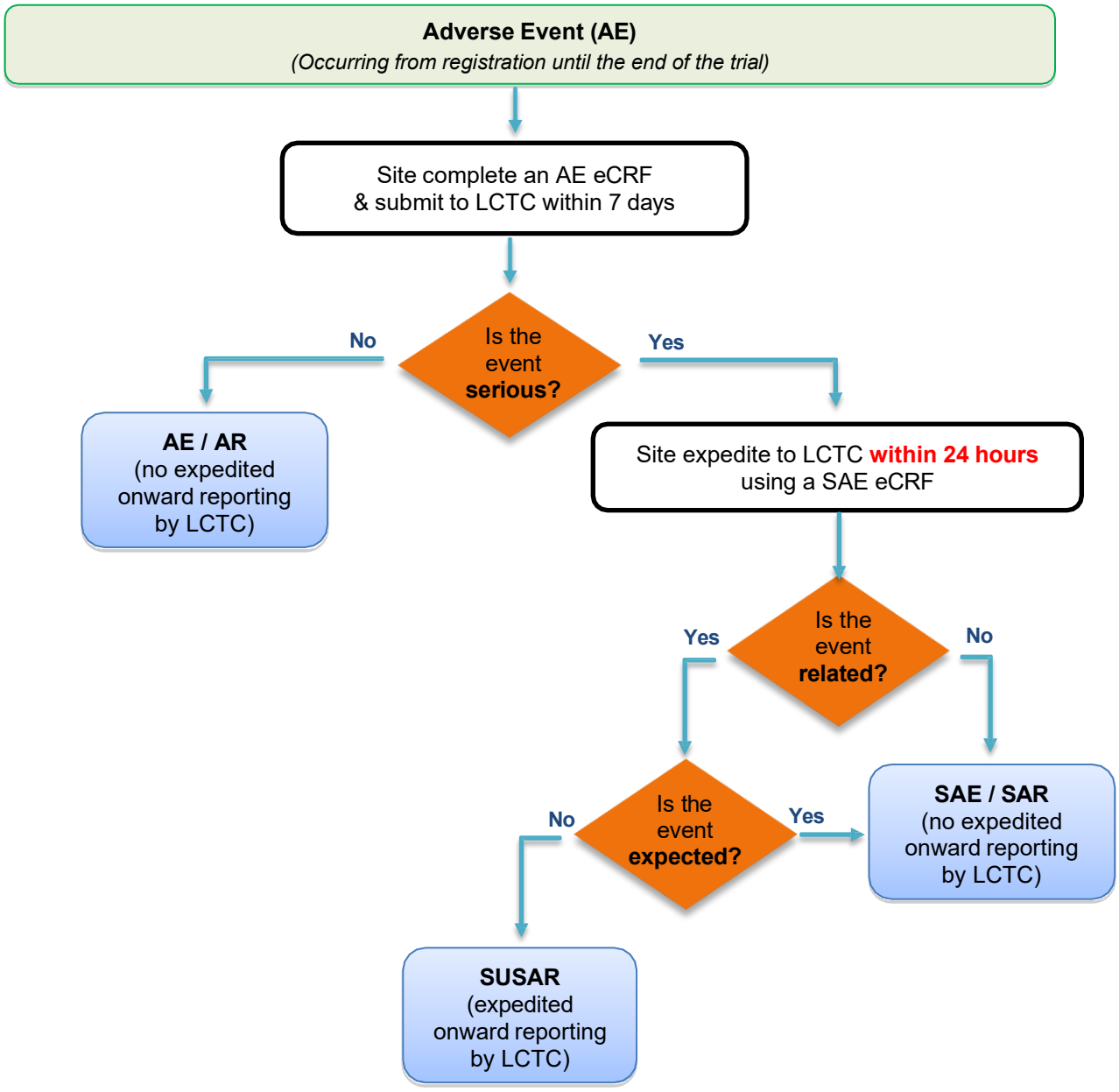
12.10 Notification of Deaths

If the research team become aware of the death of a participant (whether related to the trial or not) this should be notified to the LCTC using the Notification of Death eCRF within 24 hours of becoming aware.

12.11 Reporting Procedures

All safety events which are recorded for the study should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine study visits, from the participant’s notes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. “serious” events are to be reported to LCTC in an expedited manner). Any questions concerning adverse event reporting should be directed to the LCTC in the first instance. A flowchart is given below to aid in determining reporting procedures for different types of adverse events.

Flowchart for Site Reporting Requirements of Adverse Events



Reporting Safety Events to the LCTC

All safety events (whether or not assessed as serious / related / expected) should be recorded on an Adverse Event Form; multiple events identified at the same timepoint/visit can be recorded on one form.

Safety events which are assessed as "serious" must **also** be recorded in more detail on Serious Safety Event Forms; a single form is used for each individual event (i.e. a single diagnosis), though multiple symptoms can be recorded. Each SAE should have a corresponding record on the participant's AE form. Where additional information is received by the site after initial submission to LCTC, this should be provided on a follow-up form within 5 days. Serious Safety Event Forms collect data regarding the nature of event, date of onset, severity, corrective therapies given, outcome and causality; all serious events reported to LCTC will be reviewed by the Chief Investigator or Medical Reviewer, and assessed for causality and expectedness.

Follow-up After Adverse Events

All reportable adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting "serious" safety events the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes:

- resolved
- resolved with sequelae (specifying with additional narrative)
- not resolved/ongoing
- ongoing at final follow-up
- fatal or unknown.

12.12 Investigator Reporting Responsibilities

The PI is responsible for ensuring that all safety events requiring recording on this study (see section 12.11) which the local research team becomes aware of are reported to LCTC. It is the responsibility of the PI/Co-PI as recorded on the Delegation Log (medically qualified person) to assess the seriousness and causality of events. When documenting any adverse events, the correct medical terminology **must** be used in accordance with MedDRA.

All safety events must be recorded on an AE form and transferred to LCTC **within seven days of the site team becoming aware of the event**.

Safety events which meet the definition of "serious" must be reported in more detail to the LCTC on an SAE form or by remote data entry and reported **immediately and in no circumstances later than 24 hours from becoming aware** where they will be appropriately processed.

The SAE form should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality must be performed by a person who has appropriate medical qualification. Initial reports must provide the minimum reporting information:

The minimum information required for reporting is as follows:

- Valid EudraCT number
- Sponsor trial number
- One identifiable coded subject
- One identifiable reporter
- One SAE
- One suspect IMP (including active substance name)
- A causality assessment.

N.B. In the absence of a delegated medically qualified person the form should be completed and signed by an alternative member of the research site trial team and submitted to the LCTC. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the LCTC. The initial report shall be followed by detailed follow-up reports as appropriate.

REPORTING AN INITIAL OR FOLLOW-UP SAE
The investigator should ensure the actions below are completed for all reportable SAEs:

1. Research sites should telephone the appropriate trial manager on telephone number **0151 794 0249** to advise that an SAE report has been submitted.
2. **The SAE form should be transferred to the LCTC Central Safety Team via secure email, to LCTCSafe@liverpool.ac.uk, within 24 hours of the local team becoming aware of the event**
3. The responsible investigator must notify their R&D department of the event (as per standard local governance procedures).
4. The participant must be identified by trial number, age or month and year of birth and initials **only**. The participant's name **should not** be used on any correspondence.
5. SAEs must be subsequently followed up in line with the processes below:
    - Follow up must continue until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. N.B. Follow-up may continue after completion of protocol treatment if necessary.
    - Follow-up information is noted on a new SAE form to be transferred securely to the LCTC as soon as more information becomes available
    - Tick the appropriate box on the new SAE form to identify the type of report; this is dependent on resolution status of the SAE e.g. follow-up / final.
6. No extra, annotated information and/or copies of anonymised test results should be transmitted unless explicitly requested.

In the event that an SAE is sent electronically & securely but the sender does not receive email confirmation of receipt/download by recipient by the end of the next working day, the sender should make contact with LCTC to ensure the file was received.

Patient safety incidents that take place in the course of research should be reported to the National Reporting and Learning System (NRLS) by each participating NHS Trust in accordance with local reporting procedures.

12.13 LCTC Responsibilities

The trial Sponsor (Liverpool University Hospital NHS FT) have delegated to LCTC the duty of onward reporting of safety events to REC, Sponsor and regulatory authorities. SOPs will be followed to ensure appropriate reporting as detailed below.

All "serious" safety events will be forwarded to the designated Medical Reviewer by LCTC who will review information provided by site and for all events assessed as "related" will provide an assessment of "expectedness".

Safety events which are assessed as "serious", "related" and "unexpected" will be expedited to the REC and MHRA as a SUSAR within the following timeframes:

- SUSARs which are fatal or life-threatening – **as soon as possible and in any case no later than 7 days** after the LCTC is first aware of the event. If the initial report is incomplete, a complete report will be submitted within an additional 8 days.
- SUSARs that are not fatal or life-threatening – **within 15 days** of the LCTC first becoming aware of the event.

It is recommended that the events below are considered for expedited reporting:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the Sponsor (see section 12.7);
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the participants, such as:
- A SAE which could be associated with the trial procedures and which could modify the conduct of the trial;
- A significant hazard to the participant population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
- A major safety finding from a newly completed animal study (such as carcinogenicity).
- Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same Sponsor;
- Recommendations of the Independent Data and Safety Monitoring Committee, if any, where relevant for the safety of the participants.

Additionally, SUSARs will be reported to the trial Sponsor / IMP manufacturer Tiofarma and Royal Free IMP subcontractor within agreed timelines.
The PIs at all institutions participating in the trial will be notified of any SUSARs within a reasonable timeline as per LCTC Safety Processing Plan, and if appropriate, accompanied by a summary of the evolving safety profile of the IMP.

The LCTC will submit annual reports containing safety information to REC and MHRA.

Any concerns raised by the trial committees or inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported AEs / ARs and SARs / SAEs in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

Maintenance of Blinding in Adverse Event Reporting

Systems for reporting safety events assessed as “related” (e.g. SAR and SUSAR) should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. SAE forms allow reporting investigators to make an assessment of causality without having to unblind the participant; breaking the blind will only take place where information about the participant’s trial treatment is clearly necessary for the appropriate medical management of the participant.

Events that are assessed serious, unexpected and related to baclofen (i.e. SUSARs) will be unblinded at the LCTC prior to onward reporting to Regulatory Authorities.

Unblinding procedures are detailed in Section 8.11.

Safety Reports

Safety reports will be generated during the trial which allows for monitoring of safety event including reporting rates and safety events by both site and arm. The LCTC will send annual developmental safety update reports (DSURs)/Annual Progress Reports (APRs) containing a list of all SAEs and SARs to the IDSMC, the MHRA and main REC. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

Urgent Safety Measures (USMs)

An urgent safety measure (USM) is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC and the MHRA.

The LCTC will notify the MHRA and REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC and the MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC and the MHRA, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

Following notification, if a substantial amendment is required this must be submitted as soon as possible to the REC and ideally within two weeks to the MHRA. If the study is temporarily halted it may not recommence until authorised to do so by the REC and the MHRA. If the study is permanently terminated before the date specified for its conclusion (in the original applications to REC the MHRA), the Sponsor should notify the REC the MHRA within 15 days of the date of termination by submitting the formal End of Trial Notification.

12.14 Contact Details and Out-of-hours Medical Cover

As this IMP has a well-established safety profile, emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for BASIS participants. All participants will be provided with a contact card and copy of the information sheet which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours, the CI or delegate can provide medical advice in relation to participation using the contact details listed at the beginning of this document. The information sheet will also contain information on the usual NHS arrangements for the participant’s reference.

13 STATISTICAL CONSIDERATIONS

13.1 Sample Size

Sample Size Calculation
The maximum total sample size required for randomisation is 400 (n=100 in each arm). If a patient drops out of the study or is lost to follow up once randomised, then they will be classified as an event, i.e. not absent from drinking. There has therefore been no inflation of the sample size to account for this. The proposed sample size of 400 post randomisation is based on a one-sided overall (family-wise) type I error of 5% and 90% power of achieving significance if patients on baclofen have a 25% absolute difference in abstinence at trial end (12% control group [43] abstinent compared to 37% baclofen group abstinent).

Feasibility of Sample Size
To demonstrate feasibility in terms of patients available for recruitment, we may request data from NHS England on finished admission episodes for alcohol cirrhosis of liver (ICD10 K70.3) across the eight proposed recruitment sites. Taken together, there were >1700 episodes in 2017/18 and >1500 episodes in 2018/2019. Although we acknowledge that individual patients may account for multiple episodes, we believe the numbers are considerably above the required recruitment rate and therefore number of patients eligible for recruitment should not impact trial delivery. Furthermore, selected sites have a strong record in trial recruitment for projects across the disciplines of hepatology and alcohol (e.g. the STOPAH trial; PMID: 25901427).

13.2 Method of Randomisation

Patient allocations will be irrevocably generated upon completion of the web-based randomisation form by a delegated member of the trial research team. Allocation concealment will be ensured as the service will not release the randomisation code until the patient has been recruited into the trial; this takes place after all week 0 measurements have been completed.

13.3 Interim Analyses

The interim analysis will take place after primary outcome is collected for 50 patients in each treatment group. At the interim analysis, a logistic regression model taking account of stratification variables and treatment assignment will be used to find the test statistic for each comparison to placebo. Any treatment whose test statistic is below 0 will be dropped from further investigation. Should all test statistics be below zero, the trial would terminate due to lack of efficacy compared with placebo.

In line with most adaptive trials, the independent data safety monitoring committee (IDSMC) will review the results from the comparative analysis during a closed meeting. This meeting will only contain the independent members of the IDSMC and the statistical team responsible for producing the report. The rest of the trial team will remain blinded to the comparative analysis. The IDSMC will be asked to make recommendations following the pre-specified rules of the design which (if any) arms should be stopped and will report these to the Trial Steering Committee (TSC). The TSC will then formally make recommendations to the funder as to how the trial should proceed.

13.4 Analysis Plan

A full statistical analysis plan (SAP) will be written prior to the conduct of any comparative analysis of the treatment arms. The main features of the SAP are summarised below:

At the end of the study a logistic regression model taking account of stratification variables and treatment assignment will be used to find the test statistic for each comparison to placebo. The largest of these will be compared to the critical value (k = 2.058). Exceeding this value would correspond to a significant improvement in abstinence of the corresponding dose over placebo. Time to event outcomes will be analysed using the log rank test and Kaplan Meier plots presented with numbers at risk. A Cox proportional hazards model will be used if appropriate. Assumptions of proportional hazards will be investigated. Categorical outcomes will be analysed using Chi-square tests and continuous data will be analysed using longitudinal mixed models (adjusting for stratification factors) as appropriate.

The analysis for the trial will use an intention to treat approach and therefore participants will be analysed in the groups that they were randomised to. Adverse event data will be monitored throughout the trial and the outcomes will be presented by group at the end of the trial. There is no plan to compare the groups using any statistical tests for adverse events.

As much information as possible will be collected about the reasons for missing outcome data; this will be used to inform any imputation approaches employed in the analysis. Such methods will be fully described in the SAP.

14 DATA MANAGEMENT AND TRIAL MONITORING

For the BASIS trial the responsibilities for Data Management and monitoring are delegated to the LCTC. Separate Data Management and Trial Monitoring Plans have been developed which provide detail regarding the internal processes that will be conducted at the LCTC throughout the trial. Justification for the level of monitoring is provided within those documents and the trial-specific risk assessment. All data will be managed as per LCTC processes and in line with all relevant regulatory, ethical and legal obligations.

14.1 Source Documents

The electronic case report form (CRF) will be considered the source document for data where no prior record exists and which is recorded directly in the bespoke CRF. A BASIS source document list will be produced for each site to be kept in the ISF and provide detail of what constitutes BASIS-specific source data.

Date(s) of informed consent processes (including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically.

14.2 Data Collection Methods

Sites will be given access to the study database and eCRFs will be completed by trained members of the research who are delegated the duty on the Delegation Log. Data are to be entered into an electronic secure web-based trial specific system by approved members of the research team at site. All SAEs will be completed electronically.
Study staff named at each site will enter data from source documents corresponding to a participant's visit onto the eCRF. The eCRF is the primary data collection instrument for the study so all data requested on the eCRF **must** be recorded and all missing data must be explained. Any corrections should be made in accordance with the principles of GCP.

Questionnaires (i.e. alcohol questionnaires) will be directly entered into the eCRF.

Office for National Statistics (ONS) Death data may be requested via NHS England at the end of study. Patients' randomisation numbers, NHS/CHI numbers, DOBs, randomisation dates may be sent to NHS England (English data) and Public Benefit and Privacy Panel for Health and Social Care (PBPP-HSC) in collaboration with Public Health Scotland's electronic Data Research and Innovation Service (eDRIS) (Scottish data) where they may be linked with routine healthcare data regarding mortality. At the time of data analysis, this resource may be used if required to obtain death data from participants. Death data may be collected via NHS England/ PBPP-HSC broken down by age, sex, and cause of death. This data may be used if required to calculate rate of survival by drinking status at the end of trial participation and treatment arm.

14.3 Monitoring

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities see section 4.

Central Monitoring

There are a number of monitoring features in place at the LCTC to ensure reliability and validity of the trial data. Data will be entered into a validated database and during data processing there will be checks for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to participant rights and safety will also be regularly performed as per LCTC processes. Any suspect data will be flagged to the site in the form of data queries. Data queries can be raised and responded to in the study database, alternatively forms can be produced at the LCTC and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites should return any data query forms to the LCTC, the forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

Clinical Site Monitoring

In order to perform their role effectively, the trial coordinator and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient medical records, laboratory reports, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the PISC. In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the study protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- checking CRF and query completion practices.

14.4 Risk Assessment

A study specific risk assessment will be performed and reviewed by representatives of the Sponsor, LCTC and the Chief Investigator or designee. The risk assessment will be compliant with LCTC SOPs and will form the basis of the monitoring plans and audit plans.

14.5 Confidentiality

This trial will collect personal data (e.g. participant names, date of birth), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

eCRFs will be labelled with a unique trial screening and/or randomisation number. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the LCTC by recruiting sites. This transfer of identifiable data is disclosed in the PISC.
N.B. Consent forms must be transferred separately to any other trial documentation to ensure the pseudonymisation of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The Sponsor is registered as a Data Controller with the Information Commissioners Office.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the trial Sponsor and The University of Liverpool's Data Protection Officer and appropriate processes followed.

14.6 Quality Assurance and Control

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.
- The TC at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual centre.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

14.7 Records Retention

The retention period for the BASIS data and information is 25 years from the official End of Trial date as defined in section 10.11.

The PI at each investigational site must make arrangements to store the essential trial documents (in compliance with the principles of GCP) including the Investigator Site File, the applicable participant medical records and Pharmacy Site File for the full length of the trial's retention period and will arrange for confidential destruction at the end of this period as instructed by the LCTC.

The PI is also responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties.

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Any paper forms will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

15 REGULATORY AND ETHICAL CONSIDERATIONS

15.1 Statement of Compliance

This study will adhere to all applicable regulatory, ethical and other principles including The Medicines for Human Use (Clinical Trials) Regulations 2004 (and amendments), Principles of GCP, The Data Protection Act 2018, and the Declaration of Helsinki (1996).

15.2 Ethical Considerations

The trial will abide by the principles of the World Medical Association Declaration of Helsinki (1996) and has been designed to be as pragmatic as possible. The protocol has undergone ethical review by an independent Research Ethics Committee and has received a favourable opinion. The main ethical issues are summarised below:

- This trial involves blinded treatment provision and placebo, therefore whether placebo or active treatment (and at what dose) will not be known. Such designs are common in clinical research where there is no gold standard pharmaceutical therapy and there are no aspects of the overall design that might be considered abnormal.
- Patients will be approached by a member of the local research team during: i) admission to a secondary care setting under the care of a Hepatologist during a hospital spell in relation to their underlying liver disease or ii) assessment by the Alcohol Care Team contemporaneously managing the participants. They will be given sufficient time to consider involvement in the trial.
- Confidentiality will be maintained as outlined in section 14.5
- Heavy alcohol consumption can result in acute or chronic cognitive deficit that may impair capacity to consent. While this impairment could be short-term, recovery may be prolonged or indeed patients may not recover capacity. This research will only approach participants that have capacity to consent at baseline. However, if capacity is lost, original consent will prevail.
- We do not have provision to include people who might not adequately understand verbal explanations or written information given in English, or who have special communication needs. These individuals will not be recruited to the study.
- Participants recruited will have their blood sampled by venepuncture. Donating blood by venepuncture produces minimal risk of bruising or bleeding. This procedure will be carried out by trained, competent health professionals. All other assessments are non-invasive and carry minimal risk.

15.3 Approvals

The protocol, PISC and any proposed public-facing material will be submitted to an appropriate Research Ethics Committee (REC), MHRA, Health Research Authority (HRA) and host institution(s) for written approval.

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

15.4 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and REC and the MHRA requirements are handled based on their nature and severity.

Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

Serious breaches

A breach of the protocol or GCP is ‘serious’ if it meets the definition of being “likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial”. This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a ‘serious’ breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of ‘serious’ and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as ‘serious’ will be reported to MHRA and REC within 7 days by the LCTC on behalf of the Sponsor and notified to the TMG, IDSMC and TSC at their next meeting.

Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, MHRA, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

16 INDEMNITY

The Liverpool University Hospital NHS FT holds insurance against claims from participants for harm caused by their participation in this clinical study. However, the treating hospital continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

17 PUBLICATION AND DISSEMINATION

17.1 Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group (TMG). The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved as a minimum. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and IDSMC should be acknowledged.
Any publications arising from this research will be reviewed appropriately prior to publication.

Authorship
Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the BASIS Consortium which will also be named at the manuscript head.

17.2 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to the MHRA, REC and the Funder (NIHR). The results of BASIS will be published in high impact journals regardless of the magnitude or direction of effect.

A lay research summary will be co-produced with PPI representatives to clearly and concisely summarise the key conclusions. The findings will be promoted through press release services at involved NHS trusts and universities. The research team will utilise their membership of professional groups, such as the British Society of Gastroenterology, Liver Clinical Research Network, and Cagliari Expert Consensus Group on the use of baclofen to treat patients with alcohol use disorder, to allow quicker dissemination into the medical community. The research team will liaise with charitable organisations such as the British Liver Trust to share the lay research summary across their network and partners. Public and patient open-access forums will be identified to help publicise the lay findings summary.

17.3 Data Sharing

At the end of the trial, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank CRF) will be prepared in order to be shared with external researchers. All requests for access to the IPD will be submitted to sponsor.

18 CHRONOLOGY OF PROTOCOL AMENDMENTS

18.1 Version 3.0 (25/AUG/2023)

Summary of Amendments from Protocol V2.0 to Protocol V3.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
Front page	Front Page	ISRCTN registration number added. Research Ethics and CTA Reference numbers added.
	General information	Table added with key details on Randomisation, Clinical Queries, SAE Reporting for clarity.
	Contact details: Individuals	Contact email has been updated for Sponsor.
1	Table of contents	The table of contents has been updated.
2	Glossary	C-SSRS Screen has been added to the glossary. CTFG has been added to the glossary. WOCBP has been added to the glossary.
3	Protocol overview	<u>Target population</u> The upper age limit for the target population age has been reduced from 75 to 65 years of age. <u>Eligibility at registration</u> The upper age limit for inclusion at registration has been amended from 75 to 65 years. The requirement to have back up contact information for a significant other has been removed. Exclusion criterion concerning recent or previous multiple suicide attempts or episodes of deliberate self-harm has been removed. Exclusion criterion concerning presence of suicidal ideation at the time of registration has been removed. <u>Eligibility criteria at randomisation</u> The upper age limit for inclusion has been amended from 75 to 65 years. The requirement to have back up contact information for a significant other has been removed. Criterion to exclude recent or previous multiple suicide attempts or episodes of deliberate self-harm has been removed.

		Exclusion criterion regarding suicide ideation has been amended. Participants that have scored 3 or more on the C-SSRS Screen and have been assessed by an appropriately qualified mental health practitioner as having suicidal ideation or behaviour prior to the baseline/randomisation visit will be excluded. <u>Patient study duration</u> Reference to ONS death data has been amended to state that data may be collected only if required.
3.1	Schematic of Study Design	Additional boxes added during the 2-week run-in period to add C-SSRS Screen at days 7 -10 and complete mental health assessment if scored 3 and above. AE assessment has been added to the Baseline assessments and C-SSRS Screen as been added to all follow-up appointments.
5.3	Risk and Benefits	Further detail related to mental health practitioner assessment prior to randomisation has been amended for clarity and history of previous attempts removed. Sentence added related to C-SSRS Screen if scored 3 and above on the follow up will be unblinded and down-titrated.
6.1.1	Who is blinded?	IDSMC acronym added.
7.1	Eligibility Criteria at Registration	The upper age limit for inclusion has been amended from 75 to 65 years. The requirement to have back up contact information for a significant other has been removed. Exclusion criterion recent or previous multiple suicide attempts or episodes of deliberate self-harm has been removed. Exclusion criterion presence of suicidal ideation at the time of registration has been removed.
7.2	Eligibility Criteria at Randomisation	The upper age limit for inclusion has been amended from 75 to 65 years. The requirement to have back up contact information for a significant other has been removed. Criterion to exclude recent or previous multiple suicide attempts or episodes of deliberate self-harm has been removed. Exclusion criterion regarding suicide ideation has been amended. Participants that have scored 3 or more on the C-SSRS Screen and have been assessed by an appropriately qualified mental health practitioner as having

		suicidal ideation or behaviour prior to the baseline/randomisation visit will be excluded.
7.3	Co-enrolment guidelines	Amended to clarify that co-enrolment in a clinical trial of an investigational medicinal product is not allowed.
8.1	Introduction	For clarity, reference to titration packs has been removed and replaced with bottles.
8.5.1	Down titration at end of treatment (24 weeks)	The end-of-treatment down-titration section has been amended for clarity. Sentence related to the 10mg TDS will not require titration has been removed, as down-titration is required Example 1. Down-titration at the end of treatment table has been removed and has been replaced by table 1. A titration regime table (table 1) has been added for illustration purposes and the down-titration time has been extended for all active arms.
8.5.2	Down titration if stopping treatment early	Example 2. Down titration if stopping treatment early table has been removed. Sentence added to flag that participants with C-SSRS Screen scores of 3 or higher, will discontinue treatment and commence down-titration.
8.7	Assessment of Adherence	Sentence regarding the Brief Medication Questionnaire has been removed as the questionnaire is not used in the trial.
8.10	Overdose	Reference to a previous history of multiple suicide or self-harm episodes has been removed. 36 h amended for clarity to 36 hours.
8.11	Unblinding	CRF amended to eCRF.
9	Outcomes	Any references to Form 90 in the primary and secondary outcome table has been removed. Explanatory added related to SADQ at follow up. A typographical error has been corrected. ONS data clarification that death data may be requested at the final analysis if required.
10.1	Participant Identification and Screening	Definition of WOCBP has been added as per CTFG guidance.
10.2	Informed Consent	Definition of highly effective contraception has been added as per the SmPC.

10.4.1	Registration Assessments	A reference to Form 90 has been removed.
10.4.2	Two Week run-in	Paragraph has been included concerning the procedure of conducting the C-SSRS Screen between days 7 and 10, along with the requirement to refer participants scoring 3 or more to a mental health assessment before randomisation to assess their eligibility.
10.5.1	Baseline Assessments - Randomisation	Assessment of Adverse Events has been added.
10.7	Schedule of Assessments and Follow up	Explanatory symbol ** has been removed from the follow-up and titration 1 and 2 of the study timepoints. Reference to Form 90 has been removed. A C-SSRS Screen and Mental health assessment of scores at 3 and above has been added from the pre-randomisation visit and will continue throughout the study period. Extra column added for the SADQ questionnaire with an explanatory symbol used as **. Assessment of Adverse Events has been added to the baseline. ONS death data request has been updated. NHS Digital has been corrected to NHS England. Reference to kit replaced by bottle.
10.8	Follow up visits (Titration Visits, Weeks 1 and 2)	A C- SSRS Screen has been added and onward referral if required.
10.9	Follow-up visits (Weeks 4, 8, 16 and 24)	Sentence amended to add clarity related to the signs of suicide ideation or behaviour.
10.9.1	Efficacy Assessments	Typo in "Timeline followback" has been corrected, and the reference to Form 90 has been removed and relevant references have been provided. A sentence has been added to provide a definition of the C-SSRS Screen assessment method with appropriate references provided. References provided for the AUDIT, SADQ, PACS and APQ questionnaires.

		Additional sentence added sentence has been introduced to the SADQ to clarify that completion at follow up is only required if the participant has started drinking .
10.9.2	Urinary ethyl glucuronide (urine) sampling	Reference to Figure 1 added.
10.9.3	Safety Assessments	A reference to the Brief Medication Questionnaire has been removed.
10.10.1	Premature Discontinuation of Trial Intervention	Suicide ideation or attempted suicide has been added for clarification.
10.10.4	Loss to Follow up	A reference to significant other has been replaced by nominated contact and wording added for clarity as the nominated contact is not mandatory.
11.3	Pharmacokinetic Rich Sampling	Figure 1 has been replaced by Figure 2.
11.5	Data Collection	A typographical error has been corrected.
12	Safety Reporting	An additional sentence has been included to provide clarity on the reporting process for all SAEs.
12.1	Terms and Definitions	Definition of Unexpected Adverse Reaction has been removed.
12.2	Assessment of Seriousness	A reference to Adverse Device Effects has been removed.
12.4	Assessment of “Causality” - Relationship to Trial Treatment	The title has been updated by removing the reference to word Intervention. A reference to word Intervention has been removed and replaced with IMP in text. Further details have been added to clarify how the assessment of causality must be performed. The word "REC" has been included.
12.5	Assessment of “Expectedness”	Additional wording has been added to further clarify that medical reviewer will assess any expectedness.
12.7	Time Period for Active Monitoring of Safety Events	Additional wording has been included to provide clarity on the recording of active safety monitoring from registration until 7 days after dose administration. A new sentence has been included, stating that pregnant women will be monitored at least until the birth outcome.
12.8	Notes on Safety Event Recording	Additional information has been added to specify that details of unintentional medication overdose should not be

		recorded. Additional guidance has been added to the footnote. A note has been included to clarify that intentional overdose incidents must be reported as adverse event.
12.9	Reporting of Pregnancy	A reference to Clinical Trial Facility Guidance (CTFG) has been added. A typographical error has been corrected.
12.10	Notification of Deaths	Minor clarification on eCRF has been added.
12.11	Reporting procedures	A new flow chart has been added to offer additional clarification for the Reporting Requirements of Adverse Events at sites from registration until the end of the trial. The previous flow chart has been removed.
12.13	LCTC Responsibilities	The sentence regarding the review of all serious safety events by a medical reviewer has been corrected, and the 24-hour completion requirement upon receiving basic information has been removed. The inclusion of a reference to the section has been added to enhance clarity. Additional information has been provided to explain the reporting process for SUSARs and a reference to the trial safety processing plan and the onward reporting of any serious event to the regulatory authorities has been added.
13.1	Sample Size	The reference to ONS death data amended as the data may be collected only if required from NHS England.
14.2	Data Collection Methods	A sentence has been added to clarify that all SAEs will be completed electronically. The reference to ONS death data amended as the data may be collected only if required. NHS Digital has been changed to NHS England.
18	Chronology of Protocol Amendments	Included a summary of the protocol changes made from v2.0 to v3.0. A sentence has been added to clarify that v2.0 was submitted to the regulatory authorities and additional amendments have been requested.
19	References	References table has been updated and all PROMs references have been added.

18.2 Version 2.0 (15/NOV/2022)

Original Approved version.
Version 2 was submitted to the MHRA and REC and further amendments were requested.

18.3 Version 1.0 (11/NOV/2022)

Not submitted for approval.

19 REFERENCES

1. Davidoff RA., *Antispasticity drugs: mechanisms of action.* Annals of neurology 1985;17:107-116.
2. Lesouef N, Bellet F, Mounier G, Beyens M-N., *Efficacy of baclofen on abstinence and craving in alcohol-dependent patients: a meta-analysis of randomized controlled trials.* Therapie 2014;69:427-435.
3. Pierce M, Sutterland A, Beraha EM, Morley K, van den Brink W., *Efficacy, tolerability, and safety of low-dose and high-dose baclofen in the treatment of alcohol dependence*: a systematic review and meta-analysis. European Neuropsychopharmacology 2018;28:795-806.
4. ANSM, Cnamts, Inserm. Le Baclofène en vie réelle en France entre 2009 et 2015. *Usages, persistance et sécurité, et comparaison aux traitements des problèmes d'alcool ayant une autorisation de mise sur le marché*. In: Département des études en santé publique Ddls, des études et des statistiques, Caisse nationale de l'assurance maladie des travailleurs salariés, editor. France: ANSM; 2017.
5. Addolorato G, Caputo F, Capristo E, Domenicali M, Bernardi M, Janiri L, Agabio R, et al., *Baclofen efficacy in reducing alcohol craving and intake:* a preliminary double-blind randomized controlled study. Alcohol and Alcoholism 2002;37:504-508.
6. Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, et al., *Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis:* randomised, double-blind controlled study. The Lancet 2007;370:1915-1922.
7. Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA., *Efficacy and Safety of Baclofen for Alcohol Dependence*: A Randomized, Double-Blind, Placebo-Controlled Trial. Alcoholism: Clinical and Experimental Research 2010;34:1849-1857.
8. Colombo G, Vacca G, Serra S, Brunetti G, Carai MA, Gessa GL., *Baclofen suppresses motivation to consume alcohol in rats.* Psychopharmacology 2003;167:221-224.
9. Ameisen O.,*Complete and prolonged suppression of symptoms and consequences of alcohol-dependence using high-dose baclofen:* a self-case report of a physician. Alcohol and Alcoholism 2005;40:147-150.
10. Thomas PE., *Suppression of alcohol dependence using high-dose baclofen*: a self-case report. Progress in Neurology and Psychiatry 2012;16:30-31.
11. Müller CA, Geisel O, Pelz P, Higl V, Krüger J, Stickel A, Beck A, et al., *High-dose baclofen for the treatment of alcohol dependence (BACLAD study)*: a randomized, placebo-controlled trial. European Neuropsychopharmacology 2015;25:1167-1177.
12. Beraha EM, Salemink E, Goudriaan AE, Bakker A, de Jong D, Smits N, Zwart JW, et al., *Efficacy and safety of high-dose baclofen for the treatment of alcohol dependence:* A multicentre, randomised, double-blind controlled trial. European Neuropsychopharmacology 2016;26:1950-1959.
13. Reynaud M, Aubin H-J, Trinquet F, Zakine B, Dano C, Dematteis M, Trojak B, et al., *A Randomized, Placebo-Controlled Study of High-Dose Baclofen in Alcohol-Dependent Patients*:The ALPADIR Study. Alcohol and Alcoholism 2017:1-8.
14. Rolland B, Simon N, Franchitto N., *Safety challenges of using high dose baclofen for alcohol use disorder:* a focused review. Frontiers in psychiatry 2018;9:367.
15. Morley KC, Baillie A, Fraser I, Furneaux-Bate A, Dore G, Roberts M, Abdalla A, et al., *Baclofen in the treatment of alcohol dependence with or without liver disease:* multisite, randomised, double-blind, placebo-controlled trial. The British Journal of Psychiatry 2018;212:362-369.
16. Owens L, Thompson A, Rose A, Gilmore I, Pirmohamed M, Richardson P., *A prospective cohort study examining the effectiveness of baclofen in the maintenance of abstinence in alcohol use disorder patients attending a joint liver and alcohol treatment clinic*. Alcohol 2017;62:11-15.
17. Wuis E, Dirks M, Termond E, Vree T, Van der Kleijn E., *Plasma and urinary excretion kinetics of oral baclofen in healthy subjects*. European journal of clinical pharmacology 1989;37:181-184.
18. Agarwal SK, Kriel RL, Cloyd JC, Coles LD, Scherkenbach LA, Tobin MH, Krach LE.,*A pilot study assessing pharmacokinetics and tolerability of oral and intravenous baclofen in healthy adult volunteers.* Journal of Child Neurology 2015;30:37-41.
19. Chevillard L, Sabo N, Tod M, Labat L, Chasport C, Chevaleyre C, Thibaut F, et al., *Population pharmacokinetics of oral baclofen at steady-state in alcoholic-dependent adult patients.* Fundamental & clinical pharmacology 2018;32:239-248.
20. Marsot A, Imbert B, Alvarez JC, Grassin-Delyle S, Jaquet I, Lançon C, Simon N., High variability in the exposure of baclofen in alcohol-dependent patients. Alcoholism: Clinical and Experimental Research 2014;38:316-321.

21. Anton RF, Moak DH, Latham P., *The Obsessive Compulsive Drinking Scale:* A self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. Alcoholism: Clinical and Experimental Research 1995;19:92-99.
22. Imbert B, Alvarez JC, Simon N., *Anticraving Effect of Baclofen in Alcohol-Dependent Patients*. Alcoholism: Clinical and Experimental Research 2015;39:1602-1608.
23. O'Shea RS, Dasarathy S, McCullough AJ., *Alcoholic liver disease*. Hepatology 2010;51:307-328.
24. Thompson A, Owens L, Richardson P, Pirmohamed M., *Systematic review: baclofen dosing protocols for alcohol use disorders used in observational studies*. European Neuropsychopharmacology 2017;27:1077-1089.
25. Pessione F, Ramond MJ, Peters L, Pham BN, Batel P, Rueff B, Valla DC., *Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis.* Effect of alcoholic hepatitis, smoking and abstinence. Liver international 2003;23:45-53.
26. NCEPOD. *Measuring the Units: A review of patients who died with alcohol-related liver disease*. In: National Confidential Enquiry into Patient Outcome and Death; 2013.
27. Williams R, Aithal G, Alexander GJ, Allison M, Armstrong I, Aspinall R, Baker A, et al., *Unacceptable failures: the final report of the Lancet Commission into liver disease in the UK.* The Lancet 2020;395:226-239.
28. Manthey J, Shield KD, Rylett M, Hasan OS, Probst C, Rehm J., *Global alcohol exposure between 1990 and 2017 and forecasts until 2030:* a modelling study. The Lancet 2019;393:2493-2502.
29. Shaw JE, Sicree RA, Zimmet PZ.,*Global estimates of the prevalence of diabetes for 2010 and 2030*. Diabetes research and clinical practice 2010;87:4-14.
30. Summary of Product Characteristics: Baclofen tablets BP 10mg. Accord-UK Ltd www.medicines.org.uk/emc/product/5728/smpc last checked 28/09/2022.
31. Bell, H., et al., *Long-term prognosis of patients with alcoholic liver cirrhosis: a 15-year follow-up study of 100 Norwegian patients admitted to one unit.* Scandinavian journal of gastroentelogy, 2004. 39(9):p. 858-863.
32. Organisation, W.H., *Global health estimates (GHE).* Geneva 2019 [Available from: https://www.who.int/healthinfo/global_burden_disease/en. [Accessed 2022-06-19], 2016.
33. Bouttell, J., et al., *The Scotish alcoholic liver disease evaluation: a population-level matched cohort study of hospital-based costs*, 1991-2011. Plos one, 2016. 11(10): p. e0162980.
34. Bellis, M.A., et al., *The alchohol harm paradox: using a national survey to explore how alchohol may disproportionately impact health in deprived individuals.* BMC public health, 2016. 16(1): p. 111.
35. Magirr D, Jaki T, Whitehead J., *A generalized Dunnett test for multi-arm multi-stage clinical studies with treatment selection.* Biometrika 2012;99:494-501.
36. Clinical Trial Facilitation Group (2014) *Recommendations related to contraception and pregnancy testing in clinical trials.* Available at: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf?fbclid=IwAR3AY5Ha0ESDyqIBeUaYI9VTFWmx9bbt8NZ-80N-5ME6pkBb1UHvFsTwqIQ (Accessed: 17/09/2022).
37. Sobell, L.C, Sobell, M.B. (1992) Timeline Followback: *A technique for assessing self-reported consumption.* Available at: https://www.nova.edu/timeline/index.html (Accessed: 24/08/2023).
38. *Bjureberg J, Dahlin M, Carlborg A, Edberg H, Haglund A, Runeson B (2022). Columbia-Suicide Severity Rating Scale Screen Version: initial screening for suicide risk in a psychiatric emergency department. Psychological Medicine 52, 3904–3912. https:// doi.org/10.1017/S003329172100075.*
39. Babor, T. F., Higgins-Biddle, J. C., Saunders, J. B., & Monteiro, M. G. (2001). *The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care* (2nd ed.). World Health Organization.
40. Stockwell, T., Murphy, D., & Hodgson, R. (1983). The Severity of Alcohol Dependence Questionnaire: Its use, reliability and validity. *The British Journal of Addiction*, 78(2), 145-155.
41. Williams, B. & Drummond, D.C. (1994) The Alcohol Problems Questionnaire: reliability and validity. Drug and Alcohol Dependence, 35, 239-243.
42. Flannery, B.A., Volpicelli, J.R. & Pettinati, H.M. (1999). Psychometric properties of the Penn Alcohol Craving Scale. *Alcoholism: Clinical and Experimental Research*, 23(8),1289-1295.
43. Owens, L., et al., A prospective cohort study examining the effectiveness of baclofen in the maintenance of abstinence in alcohol use disorder patients attending a joint liver and alcohol treatment clinic. Alcohol, 2017. 62: p. 11-15.

20 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to CA and / or Ethical review are submitted as separate version-controlled documents.