AlcoChange

Real world implementation of AlcoChange: a smartphone digital therapeutic to improve outcomes from alcohol-related liver disease

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FUNDER

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Protocol Information

This protocol describes the AlcoChange Trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non- Trial participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but sites entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This Trial will adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, the current Data Protection Regulations and all other regulatory requirements, as appropriate.

CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase Level
ALT	Alanine Aminotransferase
ArLD	Alcohol-Related Liver Disease
AST	Aspartate Aminotransferase
BCI	Behavioural Change Intervention
CI	Chief Investigator
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
EQ-5D-5L	EuroQol- 5 Dimension Quality of Life Questionnaire (Long)
EU	European Union
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	Gamma-glutamyl Transferase
GP	General Practitioner
Hb	Haemoglobin
HRQoL	Health-related Quality of Life
IDMC	Independent Data Monitoring Committee
INR	International normalised ratio
ISF	Investigator Site File
MCV	Mean corpuscular volume
MHRA	Medicines and Healthcare products Regulatory Agency
NCI	National Cancer Institute
NNT	Number Needed to Treat
PI	Principal Investigator
PIS	Participant Information Sheet
PID	Personally Identifiable Data
QALY	Quality Adjusted Life Years
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCTU	Southampton Clinical Trials Unit
TLFB	Timeline Follow Back Method
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
WBC	Whole Blood Count

KEYWORDS

Alcohol-related liver disease (ArLD); digital therapeutic; smartphone; breathalyser; self-monitoring

TRIAL SYNOPSIS

Short title/Acronym:	AlcoChange
Full title:	Real world implementation of AlcoChange: a smartphone digital therapeutic to improve outcomes from alcohol-related liver disease

Population:	Inclusion criteria Adults (aged 18 years or older), with a diagnosis of alcohol-related liver disease (established cirrhosis or alcoholic hepatitis within 6 weeks) who have used alcohol within one month of being admitted to secondary care, or having been reviewed in outpatient clinic. Patients must have been clinically advised to attain abstinence, and intend to achieve abstinence. Patients must have access to an appropriate smart phone, be willing and able to give written informed consent and have sufficient English to understand the instructions for using the AlcoChange device. Exclusion criteria We will exclude anyone taking part in another interventional study, anyone referred for end-of-life palliative care and anyone referred for in-patient alcohol rehabilitation. A full list of eligibility criteria can be found in sections 7.2 & 7.3.
Primary Objective:	To evaluate the effectiveness of AlcoChange to reduce alcohol use in patients with alcohol-related liver disease (ArLD).
Rationale:	Deaths from liver disease are increasing at an alarming rate in the UK, primarily due to excess alcohol use - 80% of liver disease in the UK is due to alcohol. The recent Lancet Commission on liver disease highlighted significant variations in care for people with alcohol-related liver disease (ArLD). The 2013 National Confidential Enquiry into Patient Outcome and Death documented widespread failings in the detection and management of ArLD in the acute setting. Alcohol-related harm costs the NHS more than £3.5 billion each year. Morbidity and mortality associated with alcohol misuse accounts for more premature deaths amongst individuals of working age than cigarette smoking in the UK. Two-thirds of these deaths are due to ArLD. Ongoing alcohol use is the single most important determinant of long-term survival in ArLD. Thus, any intervention that decreases alcohol use and improves abstinence will improve mortality in this group. The current NHS care pathway for individuals admitted with alcohol-related harm is evaluation by an Alcohol Care Team. However, with the alarming rise in patients presenting with alcohol-related problems, there is increasing pressure on resources and access to Alcohol Care Teams, hence referral times are increasing and an unmet clinical need has arisen. There are no effective pharmacological therapies to maintain

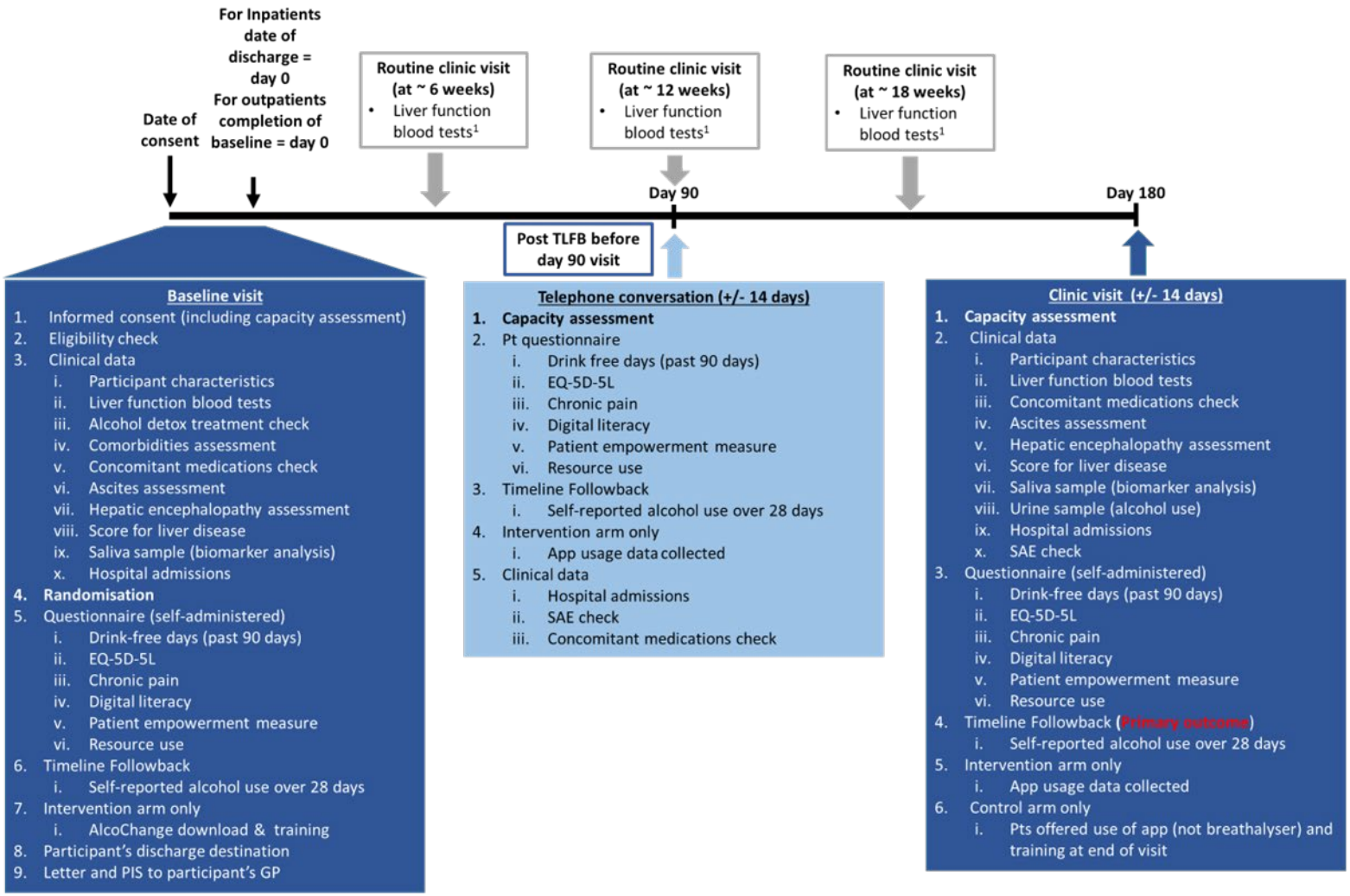
	abstinence amongst patients with ArLD. By contrast, behaviour change interventions (BCIs) are effective tools for reducing alcohol consumption in individuals without ArLD (Number Needed to Treat; NNT=8). However, only around 6% of individuals with harmful drinking receive a BCI, and this face-to-face intervention is difficult to scale. Smartphone applications as a digital therapeutic are an effective way to remotely deliver BCIs and are easily scalable. Similar approaches have been shown to provide significant benefits as part of smoking cessation interventions in a UK population.
Trial Design:	Individually randomised controlled trial; treatment allocation ratio of 1:1. The trial will involve changes in clinical processes, systems and behaviours, consequently the study includes a training and monitoring package designed to help clinical staff recruit and motivate participants to complete data collection.
Sample size :	400 participants will give us 90% power, with alpha 0.05, to detect a difference in drinking within low risk levels from 57.5% in the control group to 40% in the treatment group, allowing for up to 15% loss to follow up
Treatment:	Control arm: Usual care Intervention arm: AlcoChange plus usual care

URL for Database:	https://www.imedidata.com
URL for randomisation:	https://prod.tenalea.net/ciru/DM/DELogin.aspx

Primary Trial Endpoints:	Proportion of patients in the intervention condition, compared to the control condition, abstinent or reduced drinking to low-risk levels (<14 units/week) at 180 days (Timeline Follow Back method, TLFB).
Secondary Trial Endpoints:	At 90 days: • self-reported alcohol use over the previous 28 days (TLFB), • self-reported alcohol use over the previous 14 days (calculated from TLFB data) • self-reported drink-free days over the previous 90 days, • heavy drinking days over the previous 28 days, calculated from the TLFB and defined as ≥ 60g alcohol/day for males and ≥ 40g/day for females • app usage data, • health-related quality of life (HRQoL), measured by EuroQoL (EQ-5D 5L) questionnaire, • quality-adjusted life years (QALYs), • health care resource use and costs, • hospital admissions, • loss of capacity • Death/rehospitalisation composite. At 180 days:

	• self-reported alcohol use over the previous 28 days (TLFB) • self-reported alcohol use over the previous 14 days (calculated from TLFB data) • self-reported drink-free days over the previous 90 days, • heavy drinking days over the previous 28 days, calculated from the TLFB and defined as ≥ 60g alcohol/day for males and ≥ 40g/day for females • app usage data, • MELD score, • UKELD score, • Child-Pugh score, • health-related quality of life (HRQoL), measured by EuroQoL (EQ-5D 5L) questionnaire, • quality-adjusted life years (QALYs), • health care resource use and costs, • net monetary benefits (cost-effectiveness), • hospital admissions, • loss of capacity, • Death/rehospitalisation composite.
Exploratory Trial Endpoints:	• At baseline and 180 days: saliva sample for microbiome analysis (correlated with severity of ArLD) • At 180 days: urine sample for ethylglucoronide (alcohol metabolite) and other exploratory metabolic markers of ArLD
Total Number of Sites:	Approximately 20 UK hospitals

TRIAL SCHEMA



Baseline clinic visit = time between date of consent and date of discharge

[1] Blood data to be collected only if participant receives routine follow up

SCHEDULE OF OBSERVATIONS AND PROCEDURES

Procedure	Person undertaking the specified event	Timepoint			
		Baseline clinic visit	Data collection from routine visit (at approx. 6, 12 and 18 weeks) (+/- 14 days)	Day 90 telephone questionnaire (+/- 14 days)	Day 180 Clinic visit (+/- 14 days)
Informed Consent	**Clinician** [1]	**X**			
Assessment of participant's capacity	**Clinician**	**X**		**X**	**X**
Eligibility evaluation	**Clinician**	**X**			
Participant characteristics	**Clinician**	**X**			**X**[2]
Blood tests • Liver biochemistry • Haematology	**Clinician**	**X**[3]	**X**[4]		**X**
Alcohol detox treatment check	**Clinician**	**X**			
Comorbidities assessment	**Clinician**	**X**			
Concomitant medications check	**Clinician /Participant**	**X**		**X**	**X**
Check for presence of ascites	**Appropriately trained Clinician**	**X**			**X**
Check for presence of hepatic encephalopathy	**Appropriately Trained Clinician**	**X**			**X**
Severity scores for liver disease (MELD, UKELD, Child-Pugh)	**Calculated in database**	**X**[8]	**X**[4] **(MELD and UKELD only)**		**X**[8]
Randomisation	**Clinician**	**X**			
Send TLFB to participant	**Clinician**			**X**[5]	
Hospital admissions (notes check)	**Clinician**	**X**		**X**	**X**
Training to use AlcoChange device	**Clinician**	**X**[6]			**X**[7]
Timeline Followback (TLFB) - self-reported alcohol use over 28 days	**Clinician /Participant**	**X**		**X**	**X**
Drink-free days (DFDs)	**Clinician /Participant**	**X**		**X**	**X**
EQ-5D-5L	**Clinician /Participant**	**X**		**X**	**X**
Chronic pain questionnaire	**Clinician /Participant**	**X**		**X**	**X**
Digital literacy and patient empowerment measurement	**Clinician /Participant**	**X**		**X**	**X**
Resource use	**Clinician /Participant**	**X**		**X**	**X**
App usage data	**CyberLiver**			**X**[6]	**X**[6]
Saliva sample - for microbiome analysis	**Clinician**	**X**			**X**

Record participant's discharge destination / place of residence	**Clinician**	**X**			
Urine sample (for biomarker analysis)	**Clinician**				**X**
Serious Adverse Events check	**Clinician**			**X**	**X**

[1] Clinician = PI (including Nurse Consultants) or medically qualified doctor in line with local procedures with demonstrable and appropriate level of training. Specific duties delegated by the PI and listed on the delegation log.
[2] Only height and weight collected at Day 180 visit
[3] For inpatients, the most recent bloods during the current admission that represent the baseline ArLD. For outpatients, bloods from last discharge or last routine bloods can be used
[4]Blood data to be collected only if participant receives routine follow-up
[5] TLFB appropriate calendar month(s) posted to the participant before the Day 90 phone call. This is for reference only.
[6]If participant was allocated to the Intervention arm
[7]Participants in the control arm to be offered access to the app after the conclusion of their Day 180 clinic visit
[8]MELD only for participants with alcoholic hepatitis

NB: The Participant/legal representative is free to withdraw consent at any time without providing a reason. When withdrawn, the participant will continue to receive standard clinical care. Follow up data will continue to be collected (unless the participant/legal representative has specifically stated that they do not want this to happen).

1 INTRODUCTION

1.1 BACKGROUND

1.1.1. Burden of liver disease in the UK

Deaths from liver disease are increasing at an alarming rate in the UK, in stark contrast to most European Union (EU) countries where liver disease deaths are falling. This is primarily due to excess alcohol use - 80% of liver disease in the UK is due to alcohol. The recent Lancet Commission on liver disease called for urgent action to reduce alcohol misuse in the UK, and highlighted significant variations in care for people with alcohol-related liver disease (ArLD) [1]. In 2013, a National Confidential Enquiry into Patient Outcome and Death documented widespread failings in the detection and management of ArLD in the acute setting [2]. In particular, the report revealed missed opportunities for earlier intervention in patients with recurrent hospital admissions where alcohol misuse had not been identified or adequately managed.

Prior to the Covid-19 pandemic (see below), costs to the NHS for alcohol-related harm were in excess of £3.5 billion per year. Morbidity and mortality associated with alcohol misuse accounts for more premature deaths amongst individuals of working age than cigarette smoking in the UK [3,4]. Two-thirds of these deaths are due to ArLD[5]. Importantly, ongoing alcohol use is the single most important determinant of long-term survival in ArLD – continued drinking following diagnosis leads to ~50% mortality at 3 years, whereas with abstinence >75% are alive at 7 years [6]. Thus, any intervention that decreases alcohol use and improves abstinence will improve mortality in this group.

The current NHS care pathway for individuals admitted with alcohol-related harm is evaluation by an Alcohol Care Team. Following evaluation, measures that may be used to support patients include: counselling, psychological appraisal, and possible pharmacological intervention. Follow up is by continued self-referral, or intermittent patient contact by primary or secondary care teams. However, with the alarming rise in patients presenting with alcohol- related problems, there is increasing pressure on resources and access to

Alcohol Care Teams, hence referral times are increasing and an unmet clinical need has arisen. There are no effective pharmacological therapies to maintain abstinence amongst patients with ArLD. By contrast, behaviour change interventions (BCIs), are effective tools for reducing alcohol consumption (NNT=8) [7,8]. However, only around 6% of individuals with harmful drinking receive a BCI, and this face-to-face intervention is difficult to scale[9]. Smartphone applications as a digital therapeutic are an effective way to remotely deliver BCIs and are easily scalable. Similar approaches have been shown to provide significant benefits as part of smoking cessation interventions in a UK population[10].

1.1.2 Impact of the Covid-19 pandemic

The Covid-19 pandemic has greatly exacerbated the healthcare impacts of alcohol-related harm. Emerging international data supports a rise in alcohol use – data from the US demonstrates an increase in overall alcohol consumption as well as heavy drinking days[11]. Data from the UK is less easy to interpret, due to increase in off-trade consumption offset by the reduction in on-trade sales which were affected by lockdowns. Nevertheless, consumer evidence supports increased consumption amongst hazardous alcohol users - the heaviest buying quintile accounting for 42% of the total increase in off-trade sales[12].

The impact of the pandemic on alcohol-specific morbidity and mortality is more stark. Deaths from ARLD increased by 20.8% between 2019 and 2020, and mortality rates continue to be high[12]. This has been attributed to the reduction in availability of outpatient clinics and alcohol services during the pandemic. As such, digital therapeutics are being seen as an important tool to remotely deliver monitoring and interventions to address this sharp upturn in morbidity and mortality.

1.2 RATIONALE AND RISK BENEFITS FOR CURRENT TRIAL

1.2.1 AlcoChange

AlcoChange is a novel, patented, CE-marked digital therapeutic based on a smartphone app and breathalyser, developed with feedback from alcohol service users and validated in a pilot study in a clinical setting in the UK.

Based on EU guidance on mobile apps and devices at the time of the pilot study (Medical Devices Directive MDD93/42/EEC, the Active Implantable Directive AIMDD90/385/EEC, and the In Vitro Diagnostics Directive IVD98/79/EC), the Medicines and Healthcare products Regulatory Agency (MHRA) approved AlcoChange as an in vitro diagnostic device, rather than a medical device. AlcoChange was registered as an in vitro diagnostic device under EU regulation IVD98/79/EC and has a CE mark which is equivalent to MHRA approval. As such, the AlcoChange app and device is compliant with EU regulations.

AlcoChange allows self-monitoring of craving, alcohol use/abstinence and breath alcohol, and provides motivational messaging in response to patient triggers. Additionally, there are a number of behaviour change 'nudges' built into the app. Behaviour change interventions (BCIs), e.g. brief intervention, are effective tools for reducing alcohol consumption, but are difficult to scale widely and not always delivered at a time when the patient is receptive. AlcoChange delivers BCIs in real time, in response to patient triggers such as cravings or geographical location. Users of the AlcoChange device are encouraged to record cravings for alcohol, and in response to cravings, they are sent motivational messages containing pre-designed content including pictures of family or connecting to named supportive friends or the charity helpline 'Drinkline'. Screenshots to illustrate the flow of the app are provided in the separate app functionality document.

1.2.2 Rationale for the trial

Pilot data demonstrated ~60% dose-dependent reduction in alcohol use from baseline at 3 months, amongst individuals with ArLD who were compliant with the app (https://www.health.org.uk/sites/default/files/IFI%20R3%20final%20report_%20Royal%20Free_%20AlcoChange.pdf). Following this pilot study, the technology is now at an appropriate stage of development for real-

world clinical evaluation in a secondary care setting. Reducing admissions and mortality from ArLD is the first clinical opportunity for AlcoChange. Extrapolating from our pilot study, we anticipate healthcare cost savings of more than £130 million/year in England alone.

As previously noted, the incidence of ArLD is increasing at an alarming rate in the UK. More than 1.1 million hospital admissions associated with alcohol were recorded in 2018, which was a further increase from 2017. Despite this, only 6% of harmful drinkers receive any input from alcohol services. These individuals are also heavy users of healthcare services. At the Royal Free London, 44% of patients with an alcohol-related admission are re-admitted within 12 months, predominantly due to poor compliance and disengagement with services, leading to a high-risk of medical complications and death.

As noted above, abstinence leads to markedly improved outcomes in ArLD. However, following inpatient review of these patients by the Alcohol Care Team (ACT), follow-up is typically through self-referral to community services. High- intensity follow-up is limited to individuals with complex addiction issues. There is no dedicated alcohol rehabilitation for patients with ArLD. There is emerging evidence from the US that alcohol rehabilitation leads to improved patient outcomes in ArLD [13]. However, with the projected increase in burden of disease, it is unlikely this will be met through increasing Alcohol Care Teams. Digital therapeutics, such as AlcoChange, provide a more scalable solution for this unmet clinical need.

A potential barrier to trial success is the use of smartphones within the population with ArLD. The pilot study noted that only 50% of potential participants had a smartphone and not all these individuals were smartphone 'literate', so despite owning a smartphone they did not engage with apps or devices. However, smartphone penetrance has increased in the time since the pilot study and the smartphone-literate population is likely to have risen. Any intervention that reduces alcohol consumption in the high-risk ArLD population will lead to decreases in morbidity, mortality and associated healthcare costs.

2 TRIAL OBJECTIVES

To evaluate the effectiveness of AlcoChange to reduce alcohol use in patients with ArLD.

3 DEVELOPMENT OF THE ALCOCHANGE TRAINING AND MONITORING PACKAGE

3.1 BACKGROUND

Although fundamentally a technology intervention designed to change patient behaviour, the Trial design involves some changes in clinical processes, systems, and behaviours, such as the training of patients in the use of AlcoChange, increased patient contact and the collecting of additional data. The AlcoChange training package will be designed to enable clinical staff participating in the Trial to both recruit and motivate participating patients, and collect and share relevant data in a high-quality and consistent manner alongside their current practice.

To ensure high-quality delivery, a phased approach will be undertaken to understand current practice that could affect implementation and then tailor bespoke training sessions for site teams. Qualitative interview prior to start of the main trial and ongoing feedback during trial delivery will enable an understanding of variance between sites that might have affected Trial outcomes. There will be four phases:

3.2 PHASE I: THEORY OF CHANGE DEVELOPMENT (0-2 MONTHS)

The aim of Phase I is to develop a theory of change for this programme of research i.e. a clear articulation of the local hospital site teams' understanding and assumptions regarding the three year project, what will this trial be in reality, what actions could affect what outcomes. To ensure smooth delivery of the research programme, it will be essential to articulate what the intervention is, how it will be delivered and when. This will involve team discussions to summarise what will be needed to achieve end goals, and ensure all team members understand each other's roles. This will ensure there is common understanding across the delivery team and design is of the highest quality.

3.3 PHASE II: UNDERSTANDING SYSTEM AND DEVELOP TRAINING AND MATERIALS (2-6 MONTHS)

The aim of Phase II is to understand current care for this patient group (including variation across sites), barriers and facilitators to the smooth running of the trial, and develop the training package and associated materials for Trial delivery. We will conduct semi-structured interviews with approximately 12 healthcare staff and approximately six patients with ArLD, all recruited through participating sites.

This will provide clarity on new processes needed for both Control and Intervention stages, inform better integration of the Trial, and help explain any future variation in delivery. Staff interviews will help us understand site team attitudes, power dynamics, and motivations to participate. Patient interviews will help us understand potential barriers and facilitators to taking part in this trial. This will inform the process, content and format of training and any associated materials to be delivered in Phase III.

Potential staff participants will self-identify as being interested through responses to emails sent from the team to participating sites. Potential patient participants will be identified and recruited by alcohol specialist nurses at participating sites using the same inclusion and exclusion criteria for the Trial (see Sections 7.2 and 7.3). To ensure the information contained within the Training and Monitoring Package Participant Information Sheet and Informed Consent Form have been fully understood, it will be reiterated prior to obtaining consent and conducting the interview.

Interviews will be conducted by either in-person (following current NHS COVID safety guidance at date of interview), over the telephone, or using video technology - Microsoft Teams - (depending on preference of participants). A topic guide will be developed to guide the interviews (see draft topic guides), based on elements of the intervention and experience of the research team. Interviews are expected to last up to 60 minutes and will take place in the participants own home, workplace (for staff), university, or alternative convenient location. Each interview will be audio recorded using a digital voice recorder and transcribed verbatim (anonymised) by a professional transcription company with whom a Service Level Agreement will be put in place.

Interviews will begin to be analysed after the first interview is conducted, as such data analysis will be an ongoing process and inform subsequent interviews. Interviews will be analysed by the study team based at UCL using thematic analysis methods, using an inductive approach to coding, including searching for disconfirming evidence, increasing the rigour and validity of the analysis process.

3.4 PHASE III: DELIVERY OF TRAINING (FROM MONTH 7)

The aim of Phase III is to deliver training to staff in participating sites regarding how to recruit and train patients into the study effectively. This will ensure sufficient patients are both recruited and fully participate (e.g. participate in 90-day questionnaire, attend clinical clinic visits). The specifics of this training will depend on the findings from Phase II. For example, interactive webinars could be used to introduce the trial (e.g. design, the screening process, patient recruitment), use of the app and breathalyser, and steps for training patients to use the app.

3.5 PHASE IV: OBSERVATIONS DURING THE TRIAL (INTERMITTENT FROM MONTH 8-31)

As part of the evaluation of the running of the Trial, including semi-structured interviews (with approximately eight staff) will be conducted at trial sites delivering the intervention. These discussions will provide important information on Trial implementation and help us understand potential variance that might have affected Trial outcomes.

All field-notes data, including reflections on any conversations with staff members, will be anonymised and no identifying information about any member of staff will be recorded. Interviews will be conducted using the same procedures as Phase II (see Section 3.3 above). The interviews will explore the experience of enrolling participants into the study, and discuss the barriers and facilitators to the smooth running of the trial. The data will be analysed using the same strategy as Phase II (see Section 3.3).

4 MAIN TRIAL DESIGN

AlcoChange is a multicentre, 2-arm individually randomised controlled trial comparing usual care against usual care plus the AlcoChange intervention (breathalyser and app) in patients with ArLD. The treatment allocation ratio will be 1:1. Patients will be recruited from approximately 18 UK hospitals over 12 months.

This approach serves the implementation evaluation goal of the parent project, as all centres will have experience of the AlcoChange intervention.

The trial will have a website and use social media for promotion. This is a general 'news service' only and will not be used to recruit participants into the study.

5 TRIAL ENDPOINTS

5.1 PRIMARY OUTCOME

Proportion of patients in the intervention condition, compared to the control condition, abstinent or reduced drinking to low-risk levels (<14 units/wk) at 180 days (Timeline Follow Back method (TLFB), data collected for the previous 28 days).

5.2 SECONDARY OUTCOMES

At 90 days:

- self-reported alcohol use over the previous 28 days (TLFB)
- self-reported alcohol use over the previous 14 days (calculated from TLFB data)
- self-reported drink-free days over the previous 90 days,
- heavy drinking days over the previous 28 days, calculated from the TLFB and defined as ≥ 60g alcohol/day for males and ≥ 40g/day for females
- app usage data (for participants allocated to the intervention arm),
- health-related quality of life (HRQoL), measured by EuroQoL (EQ-5D 5L) questionnaire,
- quality-adjusted life years (QALYs),
- health care resource use and costs,
- hospital admissions,
- loss of capacity,
- death/rehospitalisation composite.

At 180 days:

- self-reported alcohol use over the previous 28 days (TLFB)
- self-reported alcohol use over the previous 14 days (calculated from TLFB data)
- self-reported drink-free days over the previous 90 days
- heavy drinking days over the previous 28 days, calculated from the TLFB and defined as ≥ 60g alcohol/day for males and ≥ 40g/day for females
- app usage data (for participants allocated to the intervention arm)
- MELD score
- UKELD score (for patients with cirrhosis),
- Child-Pugh score (for patients with cirrhosis),
- health-related quality of life (HRQoL), measured by EuroQoL (EQ-5D 5L) questionnaire,
- quality-adjusted life years (QALYs),

- health care resource use and costs,
- net monetary benefits (cost-effectiveness),
- hospital admissions,
- loss of capacity,
- death/rehospitalisation composite.

Liver function (biochemistry and haematology) blood test data will be collected at baseline and day 180, as well as at routine clinic visits at approx. 6 weeks, 12 weeks and 18 weeks after recruitment at baseline (if the participant receives routine follow-up).

5.3 EXPLORATORY TRIAL ENDPOINTS

- At baseline and 180 days - saliva sample for microbiome analysis (correlated with severity of ArLD)
- At 180 days – urine sample for ethylglucoronide (alcohol metabolite) and other exploratory metabolic markers of ArLD

6 DEFINITION OF END OF TRIAL

The trial work package will end once the last patient has delivered their last piece of follow-up data.

7 SELECTION AND ENROLMENT OF PARTICIPANTS

7.1 CONSENT

Consent to enter the trial must be sought from each participant only after a full explanation has been given, a Participant Information Sheet (PIS) offered, and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the trial for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Upon completion of the informed consent form, a copy will be given to the participant, a copy stored in the participant's medical notes and the original filed in the site trial file. A copy of the consent form should be sent to the SCTU via SafeSend to allow for central monitoring.

7.2 INCLUSION CRITERIA

1. Adults aged 18 years or older with a diagnosis of ArLD. This includes established cirrhosis (diagnosed clinically, or by imaging/transient elastography/biopsy) or alcoholic hepatitis† within 6 weeks.
2. Clinical encounter within secondary care (either inpatient admission or outpatient clinic)
3. Alcohol use within one month of clinical encounter
4. Clinical advice, and patient intent, to maintain abstinence from alcohol
5. Access to appropriate smart phone
6. Willing and able to give written informed consent
7. Sufficient English to understand the instructions for using the AlcoChange device

†Alcoholic hepatitis as defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria:

- Onset of jaundice within 60 days of heavy alcohol consumption (>50g/day, for at least 6 months)
- Serum bilirubin >51 umol/L
- Elevated aspartate aminotransferase (AST)between 50 U/L and 400 U/L
- AST:ALT (alanine aminotransferase) ratio of more than 1.5
- No other cause of acute hepatitis

7.3 EXCLUSION CRITERIA

8. Taking part in another interventional study
9. Referred for end-of-life palliative care
10. Referred for in-patient alcohol rehabilitation in a tertiary facility
11. If recruited as an in-patient, severe liver failure during inpatient stay (acute-on-chronic liver failure grades 2 or 3)
12. Multiple (>6) alcohol-related hospitalisations during the preceding 2 years

We will include participants with chronic pain syndrome (>3 months pain at single anatomical site). The data from these patients will also be used in a sub-group analysis, as the pilot study suggested these patients may have decreased response to the AlcoChange intervention.

7.4 SCREENING FAILURES

All patients screened for entry into the trial will be documented in the site screening log. The patient's post code will be coded against one of ten Index of Multiple Deprivation Decile scores by the site study team. See separate 'Index of Multiple Deprivation Decile calculator' sheet for instructions.

8 REGISTRATION/RANDOMISATION PROCEDURES

Patients will be identified by ward staff in the event of hospital admission, or by screening routine outpatient clinic lists. If the participant is an outpatient, a PIS can be sent prior to the routine clinic appointment and registration/randomisation can take place at the clinic visit. Or, the patient can receive the PIS at the time of the clinic visit and have a follow-up clinic appointment booked for registration and randomisation. The medically-trained specialist(s) will discuss the study as it is currently presented at the recruiting site and ask eligible patients to take part.

Eligibility must be confirmed prior to randomisation. Randomisation via the interactive web response system (IWRS) in ALEA will occur after all screening procedures have been carried out. Following randomisation, the patient should then be added to the trial database (RAVE) and the baseline eCRF completed.

9 CONTRACEPTION

There are no contraception stipulations as part of the trial and participants may continue to use their usual methods of contraception while taking part in the study.

10 TRIAL OBSERVATIONS AND PROCEDURES

10.1 SCREENING PROCEDURES

On reviewing the potential participant, the medically-trained specialist will assess their eligibility for the study and liaise with the wider site team delivering the trial.

10.2 TRIAL PROCEDURES

10.2.1 Baseline visit (as inpatient)

The baseline visit occurs between date of consent and date of discharge (day 0), allowing for staggered data collection during this time. Data for the patient questionnaire and TLFB can be captured post-discharge from the ward, within 7 days of discharge. However, in the event that a patient has been deemed eligible, but prematurely discharged, they must be invited back within 7 days post-discharge for completion of trial procedures, i.e. registration, randomisation and baseline procedures. In this event, day 0 will be the day the participant left the study visit post baseline completion.

- Informed consent (including clinical assessment of participant's capacity)

- Eligibility evaluation
- Participant characteristics (age, sex, height, weight, ethnicity)
- Liver function blood tests (most recent bloods during current admission that best represent baseline ArLD)
    - Serum Chemistry
        - Creatinine
        - Urea
        - AST
        - ALP
        - ALT
        - Bilirubin
        - Sodium
        - Potassium
        - Albumin
        - Calcium
        - Inorganic Phosphate
        - Total Protein
        - Glucose
        - GGT
    - Haematology
        - Haemoglobin (Hb)
        - Mean corpuscular volume (MCV)
        - WBC
        - Platelets
        - INR
        - Neutrophils
- Record if participant received alcohol detox treatment during their admission
- Record number of previous alcohol detox treatments
- Record if participant has comorbidities
- Concomitant medications check (from clinical notes or discharge summary)
- Ascites assessment
- Hepatic encephalopathy assessment (West Haven score)
- Severity scores for liver disease (MELD, UKELD, Child-Pugh – calculated in the database, MELD only for alcoholic hepatitis participants)
- Saliva sample - for microbiome analysis, correlated with severity of ArLD†
- Hospital admissions (notes check) date of consent and 90 days prior. To include current admission.
- **Randomisation**
- Timeline Followback (TLFB) - self-reported alcohol use over the previous 28 days prior to admission
    - **Please note:** At baseline, the 'End date' is the day before the participant was admitted into hospital
- Patient questionnaire:
    - drink-free days (DFDs, over the past 90 days)
    - EQ-5D-5L
    - Chronic pain questionnaire
    - Digital literacy and patient empowerment measurement questionnaire
    - Resource use questionnaire
- Other procedures
    - Training participant to use the AlcoChange device (if participant was allocated to the intervention arm)
    - Record the participant's discharge destination
    - Letter and copy of PIS to participant's GP informing them of their patient's participation

†To be stored at the study site until samples can be couriered to the central lab

- The saliva sample should be stored in the freezer at -20°C or -80°C

The local site study team will collect contact details (including 1-2 phone numbers and an email address) from all participants to enable contact during the study and to allow follow-up phone calls. Contact details will be stored securely at site in a restricted locked environment, in accordance with the General Data Protection Regulation (GDPR).

10.2.2 Baseline clinic visit (As outpatient)

The baseline visit occurs either at a routine outpatient clinic appointment, or at a follow-up clinic appointment booked specifically for the baseline visit. Time frame for the separate, trial-specific outpatient visit for baseline should not exceed four weeks since the patient was invited to consider the trial. Data for the patient must be collected before the participant leaves the clinic appointment where the baseline visit takes place.

- Informed consent (including clinical assessment of participant's capacity)
- Eligibility evaluation
- Participant characteristics (age, sex, height, weight, ethnicity)
- Liver function blood tests (recent blood tests within 6 weeks of baseline visit)
    - Serum Chemistry
        - Creatinine
        - Urea
        - AST
        - ALP
        - ALT
        - Bilirubin
        - Sodium
        - Potassium
        - Albumin
        - Calcium
        - Inorganic Phosphate
        - Total Protein
        - Glucose
        - GGT
    - Haematology
        - Haemoglobin (Hb)
        - Mean corpuscular volume (MCV)
        - WBC
        - Platelets
        - INR
        - Neutrophils
- Record number of previous alcohol detox treatments
- Record if participant has comorbidities
- Concomitant medications check (from clinical notes or discharge summary)
- Ascites assessment
- Hepatic encephalopathy assessment (West Haven score)
- Severity score for liver disease (MELD UKELD, Child-Pugh – calculated in the database, MELD only for alcoholic hepatitis participants)
- Saliva sample - for microbiome analysis, correlated with severity of ArLD†
- Hospital admissions (notes check) 90 days prior to clinic visit
- **Randomisation**

- Timeline Followback (TLFB) - self-reported alcohol use over the previous 28 days
    - **Please note:** At baseline, the 'End date' is the day before the participant's clinic visit
- Patient questionnaire:
    - drink-free days (DFDs, over the past 90 days)
    - EQ-5D-5L
    - Chronic pain questionnaire
    - Digital literacy and patient empowerment measurement questionnaire
    - Resource use questionnaire
- Other procedures
    - Training participant to use the AlcoChange device (if participant was allocated to the intervention arm)
    - Record the participant's discharge destination / place of residence
    - Letter and copy of PIS to participant's GP informing them of their patient's participation

†To be stored at the study site until samples can be couriered to the central lab

- The saliva sample should be stored in the freezer at -20°C or -80°C

The local site study team will collect contact details (including 1-2 phone numbers and an email address) from all participants to enable contact during the study and allow follow up phone calls.

10.2.3 Follow up (for all patients)

Approx. 6 weeks (+/- 14 days) after baseline visit only if done as part of standard care

- Liver function blood test data will be collected from a participant's routine clinic visit, for patients who receive routine follow up.

90 days (+/- 14 days) – telephone call

- **Please note:** Participant to be posted a copy of the TLFB and the appropriate calendar month(s) before the phone call. This is for the participant's reference only.
- Clinical assessment of participant's capacity (if participant has lost capacity do not complete any trial procedures for this visit and alert their GP; if loss of capacity is felt to be permanent then withdraw the participant from the trial and complete an End of Study form in the database)
- Patients will complete a telephone questionnaire with a member of the site study team. Member of site study team to complete the paper forms with the participant's answers.
    - Timeline Followback (TLFB) - self-reported alcohol use over the previous 28 days
    - Drink-free days (DFDs, over the past 90 days)
    - EQ-5D-5L
    - Chronic pain questionnaire
    - Digital literacy and patient empowerment measurement questionnaire
    - Resource use questionnaire
    - Concomitant medications check (participant-reported)
- Other procedures
    - App usage data will be collected (if the participant was allocated to the intervention arm)
    - Hospital admissions (notes check) from consent to 90 day visit
    - Serious Adverse Event (SAE) check

Approx. 12 weeks (+/- 14 days) after baseline visit only if done as part of standard care

- Liver function blood test will be collected from a participant's routine clinic visit, for patients who receive routine follow up.

Approx. 18 weeks (+/- 14 days) after baseline visit only if done as part of standard care

- Liver function blood test will be collected from a participant's routine clinic visit, for patients who receive routine follow up.

180 days (+/- 14 days) - clinic visit

Patients will attend a clinic visit so that primary outcome data can be collected.

- Clinical assessment of participant's capacity (if participant has lost capacity, alert their GP, withdraw the participant from the trial and complete an End of Study form in the database)
- Participant characteristics (height and weight only)
- Liver function blood tests
    - Serum Chemistry
        - Creatinine
        - Urea
        - AST
        - ALP
        - ALT
        - Bilirubin
        - Sodium
        - Potassium
        - Albumin
        - Calcium
        - Inorganic Phosphate
        - Total Protein
        - Glucose
        - GGT
    - Haematology
        - Haemoglobin (Hb)
        - Mean corpuscular volume (MCV)
        - WBC
        - Platelets
        - INR
        - Neutrophils
- Concomitant medications check (clinical notes or participant-reported, may be facilitated by recent clinic letter or discharge summary)
- Ascites assessment
- Hepatic encephalopathy assessment (West Haven score)
- Severity score for liver disease (MELD UKELD, Child-Pugh – calculated in the database, MELD only for alcoholic hepatitis participants)
- Saliva sample - for microbiome analysis, correlated with severity of ArLD†
- Urine sample for ethyl glucuronide measurement (biomarker of recent alcohol use)†
- Hospital admissions (notes check) since 90 day visit
- Site team will check for SAEs
- Timeline Followback (TLFB) - self-reported alcohol use over the previous 28 days
- Patient questionnaire:
    - Drink-free days (DFDs, over the past 90 days)
    - EQ-5D-5L
    - Chronic pain questionnaire
    - Digital literacy and patient empowerment measurement questionnaire
    - Resource use questionnaire (since 90 day visit)
- Other procedures
    - App usage data will be collected (if the participant was allocated to the intervention arm)
    - Participant receives £20 voucher 'thank you'

      Both control and intervention arm patients will be provided with a new (for control arm) or repeat prescription (for intervention arm) for AlcoChange after 180 days. The app is for their own use, and the data collected as part of this new or renewed prescription will not be used for analysis as part of the study. Patients will have the option to choose whether or not they

need the breathalyser. The sites will be provided with sufficient breathalysers to issue to patients who opt to use them. Intervention arm patients would be familiar with using AlcoChange and would not need further training. The re-prescription(s) for intervention arm patients will be enabled digitally. Control arm patients can be trained to use AlcoChange by a study staff member or can use the training video or in-app guide to set up and use the app.

†To be stored at the study site until samples can be couriered to the central lab at UCL

- The saliva and urine samples should be stored in the freezer at -20°C or -80°C

Booking Day 90 and Day 180 appointments

When contacting the patients to arrange the 90-day call and 180-day clinic visit, please attempt contact 3 times using 2 different forms of communications. If a patient is not successfully contacted for the day 90 call, the patient should still be contacted to arrange the 180-day face-to-face clinic appointment.

Long-term routine data follow-up

Participants are asked to consent to allowing the study team access to their routine data generated after the trial ends for ethically approved research.

Consenting to long-term follow-up is optional and the participant does not have to agree to it to take part in the AlcoChange trial. They can also withdraw consent for long-term follow-up at any time.

10.3 DEVIATIONS AND SERIOUS BREACHES

Any trial protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the SCTU and the local R&D Office immediately. SCTU will then advise of and/or undertake any corrective and preventative actions as required.

Any serious breaches of the protocol or of the principles of Good Clinical Practice, will be reported to the Research Ethics Committee (REC). A "serious breach" is defined as a breach of the protocol or, of the principles of Good Clinical Practice which is likely to affect to a significant degree the safety or physical or mental integrity of the research participants, or the scientific value of the research.

10.4 TRIAL DISCONTINUATION

In consenting to the trial, participants have consented to the study intervention, follow-up and data collection. Participants may be discontinued from the trial procedures at any time.

10.4.1 Reasons for Trial discontinuation

Participants may be discontinued from the trial in the event of:

- Clinical decision, as judged by the Principal Investigator or CI

Full details of the reason for trial discontinuation should be recorded in the eCRF and medical record.

10.5 WITHDRAWAL

The participant / legal representative is free to withdraw consent from the trial at any time without providing a reason.

Investigators should explain to patients the value of remaining in trial follow-up and allowing this data to be used for trial purposes. Where possible, patients who have withdrawn from trial treatment should remain in follow-up as per the trial schedule. If patients additionally withdraw consent for this, they should revert to standard clinical care as deemed by the responsible clinician. It would remain useful for the trial team to continue to collect standard follow-up data and unless the patient explicitly states otherwise, follow-up data will continue to be collected.

Details of trial discontinuation (date, reason if known) should be recorded in the electronic CRF and medical record.

10.6 PROHIBITED AND RESTRICTED THERAPIES DURING THE TRIAL

None.

11 BLINDING AND PROCEDURES FOR EMERGENCY UNBLINDING

The trial is not blinded.

12 SAFETY

12.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a participant or clinical trial participant which does not necessarily have a causal relationship with trial treatment or participation. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the trial treatment or participation (regardless of causality assessments).

Serious Adverse Event (SAE) is any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing hospitalisation***
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**
- Other important medical events**.

*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.
**Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Note: It is the responsibility of the Principal Investigator (PI) or delegate to grade an event as 'not serious' (AE) or 'serious' (SAE).

12.2 SERIOUSNESS

A complete assessment of the seriousness must always be assessed by a medically qualified doctor or who is registered on the delegation of responsibility log; this is usually the investigator.

All adverse events that fulfil the criteria definition of 'serious' in protocol section 12.1 that are not listed in the below list as a reporting exception, must be reported to SCTU using the Serious Adverse Event Report Form. Note however, that any serious event deemed possibly/potentially related to the trial processes or procedures, regardless of whether it has been listed as an exception, needs to be reported to the SCTU.

All SAEs must be reported immediately by the participating centre to the SCTU.

Hospitalisations will be captured within the eCRF and reviewed by a clinician. Any event meeting the aforementioned criteria will be reported as an SAE to the SCTU.

12.2.1 Exceptions

For the purposes of this trial, the following SAEs **do not** require reporting to SCTU using the Serious Adverse

Event Report Form unless deemed potentially related to trial processes or procedures. If unsure, the event should be reported to SCTU as an SAE.

The following events are exempt from reporting due to their expectedness within patients with ArLD:

Hepatobiliary disorders

- Decompensated cirrhosis
- Acute on chronic liver failure
- Gastrointestinal bleeding (including haematemesis, melena, variceal and non-variceal haemorrhage)
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome
- Ascites
- Pleural effusion (including hepatic hydrothorax)
- Hepatic encephalopathy
- Jaundice
- Oedema
- Bruising

Renal and urinary disorders

- Pre-renal failure

Cardiac disorders

- Cardiovascular insufficiency
- Hypotension

Respiratory, thoracic and mediastinal disorders

- Hepatopulmonary syndrome
- Portopulmonary hypertension

Infections and infestations

- Increased risk of infection
- Bacteraemia
- Fungaemia
- Sepsis

Endocrine disorders

- Osteoporosis/ Pathological fractures
- Hypoadrenalism
- Infertility
- Gynaecomastia
- Hair loss
- Amenorrhoea

Investigations

- Anaemia
- Thrombocytopaenia
- Leucopoenia
- Coagulopathy
- Elevated aminotransferases
- Elevated GGT
- Hypoalbuminaemia

- Hyperammonaemia
- Hyperlactatemia

Metabolism and nutrition disorders
- Abnormalities of serum sodium, potassium, calcium, magnesium, phosphate

Nervous system disorders
- Peripheral neuropathy
- Autonomic neuropathy
- Headache
- Seizures (including alcohol-withdrawal seizures)
- Falls (including alcohol-related falls)
- Altered conscious level and coma

Neoplasms benign, malignant and unspecified (including cysts and polyps)
- Hepatocellular carcinoma (HCC)
- All non-HCC cancer

Multiple organ failure
- Death may occur as an outcome of the complications of the underlying disease state

12.3 CAUSALITY

A complete assessment of the causality must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

If any doubt about the causality exists, the local investigator should inform the SCTU who will notify the Chief Investigator. Other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality, SCTU will classify the event as per the worst-case classification and if onward reporting is required, the applicable Research Ethics Committee will be informed of both parties' points of view.

Relationship	Description	Event Status
Unrelated	There is no evidence of any causal relationship	Not related to treatment
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 treatment). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	Not related to 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 treatment). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Related and expected SAE/ Related and unexpected SAE
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Related and expected SAE/ Related and unexpected SAE

Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Related and expected SAE/ Related and unexpected SAE

In terms of event status, **Related and expected SAE** would signify that the SAE is related to the trial treatment and is expected. **Related and unexpected SAE** would be classified as an SAE which is related to the trial treatment and is unexpected.

12.4 EXPECTEDNESS

For this trial, no SAEs are considered expected i.e. the trial processes and procedures are not expected to result in an SAE. Thus, if a SAE is deemed related to a trial process and/or procedures it will be deemed unexpected and reported to the REC.

12.5 REPORTING PROCEDURES

For the purposes of this trial, non-serious AEs will not be recorded.

All serious adverse events, unless listed as an exception in section 12.2.1 should be reported to the SCTU via the method listed in section 12.6 from date of informed consent unless otherwise specified in the protocol.

12.6 REPORTING DETAILS

For all reportable serious adverse events a SAE report form should be completed with as much detail as possible (including any relevant anonymised treatment forms and/or investigation reports) and emailed to SCTU immediately but at least within 24 hours of site becoming aware of the event.

Or

Contact SCTU by phone to report the event and then email a scanned copy of the SAE report form completed as above as soon as possible.

SAE REPORTING CONTACT DETAILS

Please email a copy of the SAE form to
SCTU within 24 hours of becoming aware of the event

Email: ctu@soton.ac.uk

FAO: Quality and Regulatory Team

For further assistance: Tel: +44(0)2381 205154 ***(Mon to Fri 09:00 – 17:00)***

Additional information should be provided as soon as possible if the event has not resolved at the time of reporting.

The SAE Report Form asks for nature of event, date of onset, grade, outcome, causality (i.e. unrelated, unlikely, possible, probably, definitely) and expectedness. The responsible investigator (or delegate) should assign the seriousness and causality.

The event term should be the most appropriate medical term of concept and grades given in accordance with the NCI CTCAE v5.

12.7 FOLLOW UP AND POST-TRIAL SAES

The reporting requirement for all SAEs affecting participants applies for all events occurring from Informed Consent up to the 180 day contact.

All unresolved SAEs should be followed by the investigator until resolved of the end of trial criteria is met (i.e. lost to follow up, withdrawal etc.). At 180 days, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's general practitioner, believes might reasonably be related to participation in this trial. The investigator should notify the trial sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated trial participation that may reasonably be related to this trial.

12.8 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO REC

SCTU will notify the REC of all **Related and Unexpected SAEs** occurring during the trial within 15 days of notification.

SCTU submit all safety information to the REC in an annual progress report.

13 STATISTICS AND DATA ANALYSES

13.1 METHOD OF RANDOMISATION

Patients will be individually randomised to either usual care or usual care plus the AlcoChange device (breathalyser and app) using ALEA on a 1:1 allocation using minimisation. Stratification factors are:

1. hospital site
2. severity of cirrhosis at baseline:
    a) No cirrhosis
    b) Child-Pugh Score A
    c) Child-Pugh Score B
    d) Child-Pugh Score C

13.2 SAMPLE SIZE

Prior work has indicated that in patients with an alcohol-related admission, standard care (review by alcohol team and brief intervention) leads to reduction of alcohol use to abstinence, or to low-risk levels, of around 40% at 180 days [14]. We assume a response rate of 40% in the control group, and 57.5% in the intervention group. This allows for up to 15% loss to follow up. 400 participants will therefore give us 90% power to detect an absolute difference of 17.5 percentage points with alpha 0.05.

Patients who die or who are hospitalised during the study period will be censored at the point of the event and will contribute no further data to the study. We assume that this will occur in approximately 15% of participants and have explicitly allowed for this in the sample size calculation.

13.3 INTERIM ANALYSES

No interim analysis is planned.

In the absence of clear evidence of harm from the intervention we do not anticipate stopping the trial early. Even if recruitment is low, experience with patients who do take part will inform the implementation, commercialisation, and other work of the project.

13.4 STATISTICAL ANALYSIS

The study will be reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines. A formal statistical analysis plan (SAP) will be written and agreed with the trial oversight committees before data lock. All data and appropriate documentation will be stored for a minimum of 10 years after the completion of the trial. All analyses will be carried out using STATA 18 or higher and/or SAS 9.4 or higher.

The primary analysis will use a mixed effects regression for a binary outcome. All models will control for appropriate baseline covariates and any stratification factors and include hospital site as a random effect, allowing for possible heterogeneity at the site level. A full list of covariates and model specification will be set out in the Statistical Analysis plan. All secondary analyses will follow a similar modelling strategy. The frequency and pattern of missing data will be presented by arm.

The primary analysis will be performed on the evaluable population defined as those who do not die before discharge. Patients who die post-discharge, experience loss of capacity in the data collection period, or have progressed to palliative care will be considered as high-level drinking (composite outcome). The hypothetical strategy (as defined in the ICH-E9 addendum on estimands) will be used for those who are abstinent due to hospitalisation, i.e., we shall consider the hypothetical scenario where abstinence due to hospitalisation does not exist. It should not be assumed that hospitalisation is due to high levels of drinking, as many hospitalisations may be unrelated to this. As hospitalisation is also anticipated to be relatively common, simply imputing a high-level of drinking (e.g., as a composite outcome) would be expected to artificially inflate the rates of high-level drinking. In the case where a participant is hospitalised at time of data collection, data prior to admission can be used where available. For 14-day timeline follow-back (TLFB), imputation methods will be used where less than 7 days of data are available (otherwise the 7+ days will be used to represent the outcome data). For 28-day TLFB, imputation methods will be used where less than 14 days of data are available (otherwise the 14+ days will be used to represent the outcome data). This may be conceptualised as representing alcohol consumption when alcohol is accessible to the individual, as close to 90 or 180 days as possible.

There are 4 pre-planned subgroup analyses: severity of liver disease (Child-Pugh score non-cirrhotic, A, B+C), Chronic pain score (yes/no) and digital literacy and patient empowerment score (continuous). These will be assessed using an interaction with treatment in the primary model.

A supplementary analysis will be carried out on those who engage with the intervention (defined as using the app at least once). A complier average causal effect (CACE) analysis will be carried out to estimate the effect of the intervention in those who use the intervention, representing a principal stratum strategy.

Adverse reactions of special interest and SAEs will be summarised by group with frequencies and percentages.

A cost-effectiveness analysis (CEA), adopting a health and personal health services perspective, will be performed using patient level data on costs and health economic outcomes collected as a part of the trial. An analysis plan for the health economic outcomes will be written and integrated with the SAP. Resource use data will be valued using appropriate unit costs to report total costs per patient for up to 180 days since randomisation. HRQoL collected using EQ-5D-5L will be combined with survival data to report QALYs at 180 days. The CEA will follow the intention-to-treat principle and report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit at 180 days. The CEA will use multilevel linear regression models that allow for clustering of patients at site. The analysis will adjust for key baseline covariates as per the primary clinical analysis.

14 REGULATORY

14.1 CLINICAL TRIAL AUTHORISATION

This trial is not considered to be a clinical trial of a medicinal product, so clinical trial authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) is not applicable.

15 ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the trial should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the trial without giving reasons must be respected.

After the participant has entered the study, the clinician may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from protocol treatment and trial follow-up without giving reasons and without prejudicing their further treatment.

15.1 SPECIFIC ETHICAL CONSIDERATIONS

The capacity of potential participants will be judged by the local hospital site staff.

15.2 ETHICAL APPROVAL

The trial protocol has received the favourable opinion of a Research Ethics Committee in the approved national participating countries.

15.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with knowledge in obtaining informed consent with reference to the patient information leaflet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the trial with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

15.4 CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the study. The investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On e/CRFs participants will not be identified by their names, but by an identification code.

16 SPONSOR

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor and this is documented in the trial task allocation matrix.

The duties assigned to the trial sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

16.1 INDEMNITY

The University of Southampton's public and professional indemnity insurance policy provides an indemnity to UoS employees for their potential liability for harm to participants during the conduct of the research. This does not in any way affect an NHS' Trust's responsibility for any clinical negligence on the part of its staff.

17 FUNDING

This study is funded by the NIHR i4i Programme (NIHR201002).

17.1 SITE PAYMENTS

The payments assigned to the trial sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

17.2 PARTICIPANT PAYMENTS

Participants will receive a £20 voucher as a 'thank you' for their time at their 180-day clinic visit. Both intervention and control arm patients can opt to receive a repeat or new prescription to AlcoChange + breathalyser (optional). Participants allocated to the intervention arm may also keep their breathalyser without opting to have a repeat prescription after 180 days.

17.3 AUDITS AND INSPECTIONS

The trial may be participant to inspection and audit by the University of Southampton (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

18 TRIAL OVERSIGHT GROUPS

The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the Trial Management Group, the Trial Steering Committee and the Data Monitoring and Ethics Committee.

18.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the study.

The AlcoChange TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

18.2 TRIAL STEERING COMMITTEE (TSC)

The TSC act as the oversight body on behalf of the Sponsor and Funder. The TSC will meet in person at least yearly and have at least one further teleconference meeting during the year. The majority of members of the TSC, including the Chair, should be independent of the trial.

The AlcoChange TSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

18.3 DATA MONITORING AND ETHICS COMMITTEE (DMEC)

The aim of the DMEC is to safeguard the interests of trial participants, monitor the main outcome measures including safety and effectiveness, and monitor the overall conduct of the study.

The AlcoChange DMEC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the DMEC, including the timing of meetings, methods of providing information to and from the DMEC, frequency and format of meetings, statistical issues and relationships with other trial committees.

19 DATA MANAGEMENT

Participant data will be entered remotely at site and retained in accordance with the current Data Protection Regulations. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudonymised by assigning each participant a participant identifier code which is used to identify the participant during the trial and for any participant- specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff.

The Participant Information Sheet and Informed Consent Form will outline the participant data to be collected and how it will be managed or might be shared; including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned will be granted access to the electronic case report forms (eCRF). ECRF completion guidelines will be provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorised by them should enter or change data in the eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. The original laboratory reports must be retained by the Investigator for future reference.

19.1 DATA COLLECTION AND STORAGE

Any personal data we collect in this study will be used only for the purposes of carrying out our research and will be handled according to the University's policies in line with data protection law. If any personal data is used which could identify a patient directly, it will not be disclosed to anyone else without the consent of the patient unless the University of Southampton is required by law to disclose it.

Data protection law requires us to have a valid legal reason ('lawful basis') to process and use Personal data. The lawful basis for processing personal information in this research study is for the performance of a task carried out in the public interest. Personal data collected for research will not be used for any other purpose.

For the purposes of data protection law, the University of Southampton and CyberLiver Ltd are joint 'Data Controllers' for this study, which means that they are responsible for looking after personal information and using it properly. The University of Southampton will keep identifiable information for 10 years after the study has finished, after which time any link between a patient and their information will be removed. Patient app data can be archived in the CyberLiver servers on a request basis, rendering the data invisible. The recruiting hospital will keep identifiable information about patients from this study for 10 years after the study has finished.

To safeguard the rights of patients, only the minimum personal data necessary to achieve our research study objectives will be used. Data protection rights – such as to access, change, or transfer such information - may be limited, however, in order for the research output to be reliable and accurate. The University will not do anything with personal data that would not be reasonably expected.

Data collected by the secure app is entered by the patient and stored on the device in encrypted form. This data will be transferred from the device to CyberLiver's secure cloud servers in encrypted form, and stored in encrypted form on in a HSCN-compliant cloud environment. CyberLiver's employees will not have access to this encrypted data and CyberLiver will not share the data with any third party.

A Data Management Plan (DMP) providing full details of the trial specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, CRF tracking and central monitoring for active trial management created.

Data queries will either be automatically generated within the eCRF, or manually raised by the trial team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the trial after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the eCRFs. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

Data may be requested from the Data Access Committee at SCTU. Any request will be considered on a monthly basis.

Hospital staff and patients who self-select for qualitative interviews will send their interview ICF to the AlcoChange team at SCTU via Safesend. This will be emailed securely to the team at UCL responsible for the qualitative interview work. The UCL team will email the potential interviewees to arrange their interview, which will be conducted over the phone or Teams, depending on interviewee preference. The interviews will be recorded and once they have been transcribed and checked for accuracy, the transcript will be stored in an anonymised form in a password encrypted folder within the 'UCLData Safe Haven', the original recording will be deleted, as will interviewee personal details.

19.2 DATA SHARING REQUESTS FOR RESULTS THAT ARE AVAILABLE IN THE PUBLIC DOMAIN

In order to meet our ethical obligation to responsibly share data generated by interventional clinical trials, SCTU operate a transparent data sharing request process. As a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

20 MONITORING

20.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at SCTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to SCTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a

number of monitoring features in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan.

The DMEC also have responsibility for specific central monitoring activities.

20.2 CLINICAL SITE MONITORING

No onsite monitoring is planned for this study. Monitoring visits may be triggered if there are concerns with a site.

On receipt of a written request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account data protection regulations). Access should also be given to study staff and departments.

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the study, including representatives of the Competent Authority. Details will remain confidential and participants' names will not be recorded outside the study site.

20.3 SOURCE DATA VERIFICATION

On receipt of a written request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account data protection regulations). Access should also be given to trial staff and departments.

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the study, including representatives of the Competent Authority. Details will remain confidential and participants' names will not be recorded outside the trial site without informed consent.

20.3.1 Source data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The AlcoChange Investigator Source Data Location Agreement (found within the Investigator Site File) details what is considered source data for the trial.

21 RECORD RETENTION AND ARCHIVING

Trial documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. All source documents will be retained for a period of 10 years following the end of the trial.

Sites are responsible for archiving the ISF and participants' medical records.

The Sponsor is responsible for archiving the TMF and other relevant documentation.

22 PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible.

Individual investigators may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG} has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors then a 'writing committee' will be identified.

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APPENDICES

24 SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
V1	First version of the protocol
V2	Changes following Sponsor and SCTU QA assessment: revised safety section; explanation for long-term follow-up added
V3	• New exclusion criteria: exclude patients referred for rehabilitation after discharge • Capacity assessment added to visit schedule • Specified MELD, UKELD and Child-Pugh as outcomes • Removed CLIF-C ACLF outcome • 'Loss of capacity' added as an outcome at d90 and d180 • 'Day 0' defined as date of discharge from hospital • Trial schema updated • Participants who die between date of consent and date of discharge to be excluded from analyses • Participants who lose capacity to be withdrawn and their GP alerted • Typographical errors corrected
V4	• V4 was not used/finalised.
V5	• Study design changed to individually randomised trial • Specifies routine blood data (at ~6/12/18 weeks) to be collected only if participant receives routine follow up • Inclusion criteria 2. changed to: **Non-elective admission** with ArLD (alcoholic hepatitis or cirrhosis – diagnosed clinically or by imaging/biopsy)" • Exclusion criteria 3. Changed to: Referred for **in-patient alcohol** rehabilitation • Added paragraphs re pandemic and covid mitigation (1.1.2) • Collecting information about participant's alcohol detox treatment during baseline admission • RNs to post a paper copy of TLFB calendar to Pts before 90 day call (for Pt reference only) • Collecting participants' height and weight (for BMI calculation) at 180 days • Collecting deprivation decile of patients' postcodes at screening • Recording participants' discharge destinations following their baseline admission • Participants in the control arm offered use of the app at 180 day visit (data not collected for trial analysis(• Pre-planned sub-group analyses added (13.4) • Collecting data about participants' comorbidities at baseline • Collecting data about participants' concomitant medications at baseline, 90 days and 180 days • New secondary outcomes added:

	○ TLFB over 14 days at 90 days and 180 days (calculated from TLFB calendar) ○ Death/rehospitalisation composite • Digital literacy tool added to participant questionnaire as part of the Patient empowerment measure
V6	• Section 19 – Insertion of new paragraph 19.1 to provide clarification on data collection and storage. • Old paragraph 19.1 becomes 19.2
V7	• Removal of co-investigators no longer on the trial • Any adult 18 years or older with ArLD in contact with secondary care, or patients screened in outpatient clinic appointments who have used alcohol in the last month to be considered • Change to exclusion criteria 'referred to palliative care' to 'referred to palliative care for end-of-life care' • Logistics for recruitment of outpatients added • Timeframes for what bloods sites can use for data collection clarified • Edit to trial schema to indicate outpatients 'day 0' • Change of use of 'nurse/doctor' to 'clinician' in the schedule of observations and procedures • Allowance of prematurely discharged patients to return with 7 days of discharge for trial procedures • Recording number of previous alcohol detox treatment added • Parameters for follow up procedures at D90 and D180 visits. • Clarification of withdrawal criteria • Adding of expectant events exempt from SAEs • Removal of reference to sites sharing patient contact numbers to SCTU • Updated number for Quality to the generic CTU number
V8	• Changes to the Statistics and Data Analyses • Changes to inclusion criteria – further definition of ArLD-associated conditions, and addition of intent to maintain abstinence • Changes to exclusion criteria – further definition of in-patient alcohol rehabilitation, and addition of further criteria: if inpatient recruit, severe liver failure during in-patient stay and multiple alcohol-related hospitalisations in preceding 2 years. • Reference to new randomisation process IWRS (ALEA) • Clarification of windows for hospital notes check and Resource Use Questionnaire • Additional guidance around loss of capacity at 90-day visit • Addition of expected events exempt from SAEs • Additional detail around patients receiving/continuing to use the App after 180-day visit