Trials

STUDY PROTOCOL

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Real world implementation of AlcoChange, a smartphone digital therapeutic to improve outcomes from alcohol-related liver disease: protocol for an individually randomised parallel group controlled trial

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Abstract

Background Deaths from alcohol-related liver disease (ARLD) are rising in the UK, representing a significant public health crisis. Effective interventions are urgently needed to reduce alcohol consumption and improve outcomes for individuals with ARLD. While behaviour change interventions (BCIs) are effective, their scalability is limited. Digital therapeutics offer a promising avenue for delivering BCIs remotely and at scale. AlcoChange, a novel digital therapeutic combining a smartphone app and digital breathalyser, delivers personalised BCIs based on patient triggers. Preliminary data suggest its potential efficacy in reducing alcohol use.

Methods This is a multi-centre, two-arm, parallel-group, individually randomised controlled trial comparing usual care (review by a hospital Alcohol Care Team and brief intervention) with usual care plus AlcoChange in patients with ARLD.

Population Adults aged 18 years or older with a diagnosis of ARLD (including cirrhosis, fibrosis, steatohepatitis, or recent alcoholic hepatitis) who have been advised to abstain from alcohol and intend to do so, and who have access to a smartphone.

Intervention Usual care plus AlcoChange, comprising a smartphone app and digital breathalyser delivering personalised behaviour change techniques.

Comparison Usual care alone.

Outcome The primary outcome is the proportion of patients abstinent or reporting low-risk alcohol consumption (< 14 units/week) at 180 days post-randomisation, assessed using the Timeline Follow-Back (TLFB) method. Secondary outcomes include self-reported alcohol use at various time points, liver disease severity, health-related quality of life, healthcare resource utilisation, and cost-effectiveness. Four hundred participants will be recruited from up to 18 NHS

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hospitals in England and randomised 1:1. A mixed-methods approach was used to develop the trial protocol, including a theory of change framework and bespoke training materials for the TLFB assessment.

Discussion This trial will evaluate the real-world efficacy and cost-effectiveness of AlcoChange in reducing alcohol consumption and alcohol-related harm in individuals with ARLD. The study addresses the urgent need for scalable interventions to combat the rising burden of ARLD in the UK. The pragmatic design and mixed methods approach to implementation aim to enhance the generalizability and impact of the findings. The trial will provide valuable evidence to inform clinical practice and policy regarding the use of digital therapeutics for alcohol use disorder and liver disease.

Introduction

Background

Deaths from liver disease are increasing at an alarming rate in the UK, in stark contrast to most EU countries where liver disease deaths are falling [1]. This is primarily due to excess alcohol use—80% of liver disease in the UK is attributed 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 hospital 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, costs to the NHS for alcohol-related harm were in excess of £3.5 billion per year. Since then, death rates have increased markedly; alcohol-related deaths in the UK were 27.4% higher in 2021 than in 2019, with the vast majority attributed to ARLD. Currently, in the UK, alcohol use accounts for more premature deaths amongst individuals of working age than cigarette smoking [1, 3]. Importantly, following a diagnosis of liver disease, *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 [4]. Thus, any intervention that decreases alcohol use and improves abstinence will improve mortality in this group.

Models of care for alcohol-related hospital admissions vary globally; in the UK, the aim is for the majority of alcohol-related admissions to be reviewed by a hospital Alcohol Care Team (ACT). These teams are multi-disciplinary teams of healthcare professionals with expertise in interventions for alcohol use disorder, including the following: counselling, psychological appraisal, and pharmacological interventions. The ambition in the NHS Long Term Plan (2019) was for ACTs to be rolled out across NHS hospitals, although the implementation of this has been hampered by the Covid-19 pandemic. Indeed, with the alarming rise in patients presenting with alcohol-related problems, there is increasing pressure on existing resources and ACTs and novel approaches are required. In patients with established liver disease, many pharmacological agents are contraindicated, and none have demonstrable efficacy. By contrast, behaviour change interventions (BCIs) are effective tools for reducing alcohol consumption (number needed to treat = 8) [5, 6]. However, only around 6% of individuals with harmful drinking receive a BCI, and this face-to-face intervention is difficult to scale [7]. 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 [8].

Rationale for the current study

The AlcoChange device

AlcoChange is a novel, patented, CE-marked digital therapeutic based on a smartphone app and digital breathalyser, developed with feedback from alcohol service users and validated in an open-label, single-centre study in a clinical setting in the UK [9]. AlcoChange is based on behaviour change theory, utilising a number of behaviour change interventions to increase the likelihood of abstinence and engagement with health-promoting behaviours. Specifically, AlcoChange allows self-monitoring of craving, alcohol consumption or abstinence, and provides motivational messaging in response to patient triggers. Behaviour change interventions (BCIs), such as 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 allows the delivery of BCIs in real time, in response to patient triggers.

Rationale for the trial

Data from the open-label study demonstrated ~ 60% dose-dependent reduction in alcohol use from baseline to 3 months, amongst individuals with ARLD

who were compliant with the app [9, 10]. Additionally, the compliant group had a significantly higher proportion achieving complete abstinence at the end of therapy and a significant reduction in alcohol-related re-admissions in the 12 months following therapy, compared with the non-compliant group. Accordingly, the technology is now at an appropriate stage of development for real-world clinical evaluation in a secondary care setting. Extrapolating from these existing data, we anticipate healthcare cost savings of more than £130 million/year in England alone.

The primary aim of this trial is to determine the real-world efficacy and cost-effectiveness of AlcoChange in reducing alcohol consumption, and consequently alcohol-related harm, in patients with established ARLD.

Methods and analysis

Design

The overall project was broken down into two major components. The first was establishing a theory of change for implementation of the trial protocol and designing a training package for the specifics of the AlcoChange intervention and the trial procedures. The second was delivery of the randomised controlled trial. All protocol amendments were approved by the REC/IRB and disseminated to trial centres. A phased approach was undertaken to understand current practices that could affect implementation of the trial protocol, and then tailor bespoke training sessions for sites. The three phases were:

Phase I Theory of change development. Two theory of change workshops were carried out with members of the trial management group, including PPIE representation, to co-produce a theory of change for the trial following current improvement science approaches (see Fig. 1)[11–13].

Phase II Understanding system aspects and developing training materials. Nine semi-structured interviews were undertaken to understand the current care pathways for this patient group (including variation across sites), as well as barriers and facilitators to the smooth running of the trial. Thematic analysis of interviews informed the development of training materials, which were subsequently tested with participant sites in two pilot workshops.

Specifically, the chosen tool to measure alcohol consumption (as the primary outcome, see below) was the Timeline Follow-Back (TLFB) method. This is an interview technique that asks respondents to provide retrospective estimates of daily drinking over a pre-specified period. To aid recall, a calendar format and noting of 'anchoring' events is used. The TLFB has been widely evaluated in different populations, including liver disease, and has been accepted as a valid assessment tool for alcohol-focused trials by regulatory bodies (e.g. FDA). However, there is relatively little experience with TLFB within the UK; only one completed study has published experience with TLFB in an NHS setting [14]. Moreover, the only available training tools for TLFB were from North

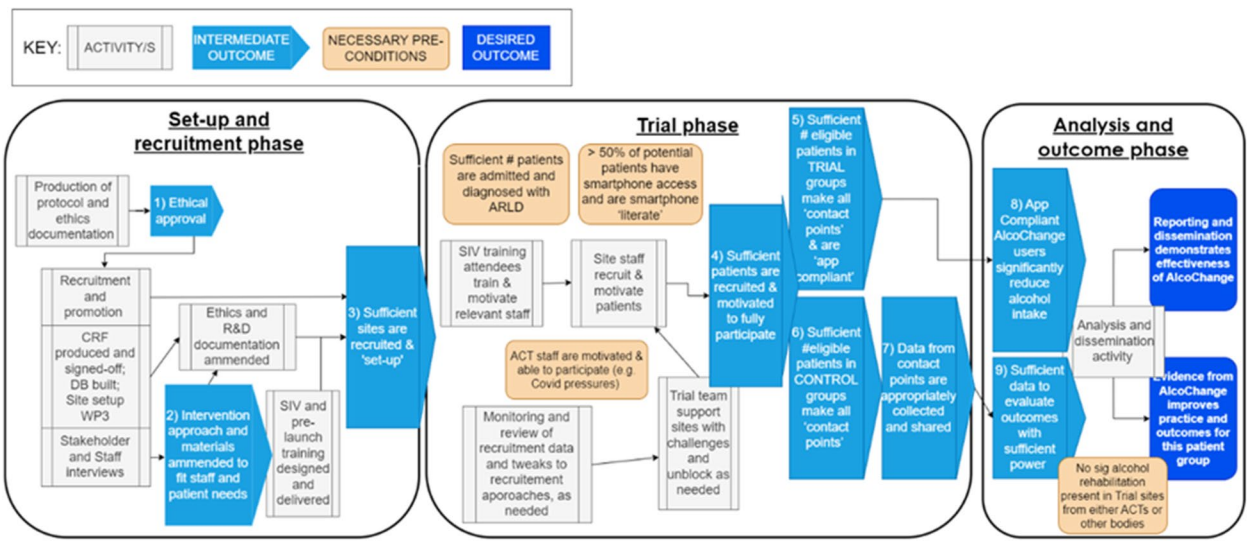

Fig. 1 Theory of Change for the Alcochange Intervention: This figure demonstrates the necessary activities (clear boxes) and contextual pre-conditions (orange boxes) needed to achieve the necessary intermediate outcomes (light blue boxes) and, in turn, the desired outcomes to be achieved (dark blue boxes)

America, thus presenting a cultural gap for implementation in an NHS setting. Consequently, the development of new, UK-focused training materials for TLFB was highlighted as a priority.

Three semi-structured interviews were carried out, with patients and NHS staff, to understand the potential barrier to implementing the TLFB method. Training materials, including two videos—AlcoChange training and TLFB—were developed and tested in pilot sessions with two AlcoChange sites.

Phase III Delivery of training. Findings from phase I and II will be integrated into site initial visit (SIV) process for all sites. Subsequently, quarterly 'drop-in' virtual meetings will be held to give all site members the opportunity to discuss any barriers to implementation of the trial.

The second component is an assessment of the clinical effectiveness of the intervention. This is a multicentre, 2-arm, parallel group, 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 up to 18 hospitals in England over 12 months.

A stepped-wedge cluster design was initially considered in order to guard against contamination between treatment arms. However, implementation of a stepped-wedge design was considered particularly challenging in the post-pandemic environment. Additionally, following discussion with the trial steering committee, the risk of contamination was thought to be sufficiently low to justify an individually randomised trial.

Trial objectives

Primary objective: To evaluate the effectiveness of AlcoChange to reduce alcohol use in patients with alcohol-related liver disease (ArLD).

Secondary objectives: To determine the effect of use of AlcoChange on liver disease severity, health-related quality of life, health care resource use, and cost-effectiveness.

Study setting

NHS hospitals in the UK with an alcohol care team.

Eligibility criteria

Inclusion and exclusion criteria are shown in Table 2. Data from patients with chronic pain syndrome (>3 months pain at single anatomical site) will also be used in a sub-group analysis, as the open-label study suggested these patients may have decreased response to the AlcoChange intervention[10].

Recruitment

Patients will be identified from two sources. Inpatients are identified as using excessive alcohol by their regular clinical teams and as part of standard practice referred to the hospital alcohol care team. The alcohol care team will review eligibility, and if appropriate discuss the trial with the patient. Outpatients attending hepatology clinics will be reviewed for eligibility for the study by their treating physician.

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. The study will be discussed with the patient by an appropriate trained physician, research nurse, or alcohol care nurse. Signed participant consent should be obtained. In addition, consent to collect samples of saliva and urine will be sought. A patient can consent to enter the study, but withhold consent for biological samples. 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 or 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 or from follow-up without giving reasons and without prejudicing further treatment. Participants receive a £20 shopping voucher at completion of the study to promote retention; this voucher can only be redeemed in shops that do not sell alcohol.

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.

Randomisation

Patients will be individually randomised to either usual care or usual care plus the AlcoChange device (breathalyser and app) according to a 1:1 allocation using minimisation, using a computer-generated sequence in ALEA [15]. The randomisation system will ensure allocation concealment by requiring eligibility information to be input prior to an allocation. Minimisation factors are:

1. Hospital site
2. Severity of liver disease at baseline:

i. Child-Pugh Score = A, and/or patients without established cirrhosis
ii. Child-Pugh Score = B
iii. Child-Pugh Score = C

The trial is not blinded. The intervention is moderated through a device and a program running on a smartphone. There is no plausible way to mask a patient who is aware of the underlying hypothesis to their study allocation.

Usual care

Usual care for this patient group will be conducted in accordance with NICE guidelines. This represents current best practice in the UK and thus is an appropriate comparator for a pragmatic trial. In a secondary (acute hospital) setting, this represents review by a member of the ACT and delivery of a BCI (brief intervention). A BCI is a short session (possibly of only a few minutes) of structured alcohol advice from an appropriate professional [6]. Features of alcohol dependence are screened for, and medically assisted alcohol withdrawal (detox) is prescribed if indicated. Onward referral to a residential alcohol rehabilitation facility was considered an exclusion criterion since it is beyond 'usual care' for this group.

Intervention

Based on European Union (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 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 are compliant with EU regulations.

AlcoChange comprises nine behaviour change techniques (BCTs) which are integrated into the mechanism of action of the smartphone app and device. During a baseline assessment, data is collected regarding the patient's health status, drinking patterns, triggers for craving and alcohol use, and motivational factors for abstinence. These data are then processed by the cloud-based decision platform to deliver BCIs in real time, in response to patient triggers. Specific examples of BCTs and interaction with the platform are listed below.

Readiness to change (BCT1) and Goal Setting (BCT2): Assessing levels of motivation and confidence, and incremental goal setting throughout the treatment period, enhances self-efficacy and empowers patients to understand drivers for change and abstinence.

Self-monitoring (BCT4): AlcoChange facilitates self-monitoring through a digital breathalyser to record blood alcohol content (BAC) and demonstrate abstinence, as well as monitoring of cravings and response to therapy.

Feedback and motivation (BCT6): Personalised reminders are sent based on patient progress (goals achieved, cravings overcome etc.). Empathy and normative feedback are used to boost motivation and facilitate engagement if goals are not met, and positive messaging is used when abstinence goals are achieved.

Replacement activities (BCT7): In response to cravings, AlcoChange nudges the patient to assess and reflect on triggers for craving, and recommends personalised replacement activities and/or coping strategies based upon data gathered at baseline.

There were no prospective rules to stop the study or modify the study interventions.

Participant schedule

Participants may be recruited from both inpatient and outpatient settings (Trial schema; Fig. 2). For inpatients, 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 timeline follow-back (TLFB; primary outcome) can be captured post discharge from the ward but must be collected before the participant leaves the hospital.

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. Patients who do not attend for scheduled study visits will be contacted using these details. Compliance with the intervention can be assessed in the control arm by monitoring use of the app, but in the current version of the app and device, such data is not available in real time to clinicians.

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 a reduction of alcohol use to abstinence, or to low-risk levels, of around 40% at 180 days [16]. 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. Four hundred participants will therefore give us 90% power to detect an absolute difference of 17.5 percentage points with alpha 0.05.

Data management

App specific data will be helped by Cyberliver in their standard backend platform. All trial specific data will be handled in a MediData RAVE database. Other than the

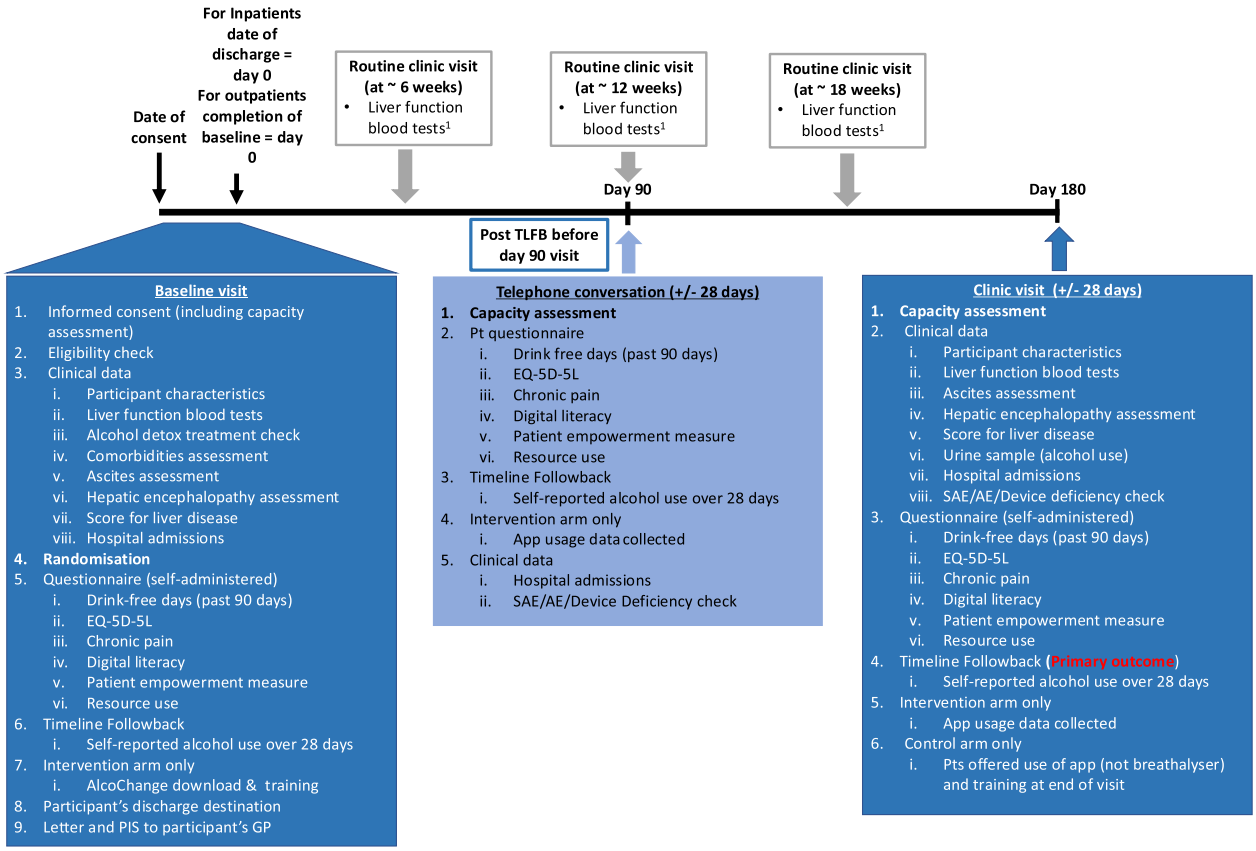

Fig. 2 Trial schema

Timeline follow Back questionnaires, trial specific data will be entered in electronic forms, directly into the database. TLFB will be completed on paper, then scanned and securely electronically transferred to the clinical trials unit. Trials unit staff will transcribe TLFB data into the database, with the original forms filed securely. The primary study database is continually backed up by the vendor. To protect participant confidentiality, all data contained in the database are linked to a unique participant code; the key is maintained in the secure digital drive accessed only by clinical study team members. Any data presented externally will be in aggregate and coded and will not include individual participant data.

Adverse events

An adverse event is any untoward medical occurrence in a participant or clinical trial participant which does not necessarily have a causal relationship with trial treatment or participation. Information on adverse events will be collected on all enrolled patients. An event which meets the criteria as a serious adverse event will be reviewed by the site principal investigator, who will take a view on whether the study intervention contributed to the event. The review will be reported to the CTU, then reviewed by the chief or co-chief investigators. If necessary, the study governance committees will be informed, and appropriate regulators notified.

Outcomes and rationale

The outcomes of interest are shown in Table 1. The primary outcome is the proportion of patients in the intervention arm, compared to the control arm, that are abstinent or have reduced alcohol consumption to low-risk levels (< 14 units/week) at 180 days. The aim of treatment in ARLD is complete abstinence from alcohol, and intention to achieve abstinence is an inclusion criterion. However, the primary outcome includes reduction of alcohol use to low-risk levels as a pragmatic outcome associated with clinical benefit [20]. Importantly, the patient-facing material for the trial does not contain any mention of reduction to low-level drinking as a positive endpoint, to avoid any misconception that this is an acceptable treatment goal in ARLD.

Table 1 Outcomes to be measured in Alcochange

Outcome type	Description	Measured by
Primary outcome	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 post randomisation	Timeline Follow Back method, (TLFB), data collected for the previous 28 days
Secondary outcomes, assessed at 90 ± 14 and 180 ± 14 days post randomisation	Self reported alcohol use over the previous 28 days	Calculated from TLFB data
	Self reported alcohol use over the previous 28 days	Calculated from TLFB data
	Self reported drink-free days over the previous 90 days	Patient report
	Heavy drinking days over the previous 28 days, defined as ≥ 60 g alcohol/day for males and ≥ 40 g/day for females	Calculated from TLFB data
	App usage data (for participants allocated to the intervention arm)	Automatically collected by Cyberliver
	health-related quality of life	EQ-5D-5L
	Accumulated QALYs	Computed from the HrQoL data
	Chronic pain	Chronic pain questionnaire, if patient able to complete
	Patient empowerment	SUSTAINS questionnaire
	Digital literacy	SUSTAINS questionnaire
	Healthcare resource use and costs	Resource use questionnaire
	Hospital admissions	Patient records
	Loss of capacity	Assessment in clinic
	Death	Patient records
	Rehospitalisation	Patient records
Explanatory endpoints	At baseline and 180 days—saliva sample for microbiome analysis (correlated with severity of ArLD)	Metagenomic sequencing
	At 180 days—urine sample for ethyl glucuronide (EtG, alcohol metabolite) and other exploratory metabolic markers of ArLD	Urine assay (mass spectrometry)

Analysis

The study will be reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines [17]. A formal statistical analysis plan (SAP) will be written and agreed with the trial governance committees before data lock.

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 SAP. Secondary analyses will follow a similar modelling strategy, with a distribution suitable to the outcome.

The primary analysis will be performed on the evaluable population, defined as those who do not die before discharge (i.e. principal stratum strategy for death prior to discharge, according to the ICH-E9 (R1) addendum on estimands). At this point, a participant has not had an opportunity to use the app and has received only brief training, so no differences are expected between arms (and therefore no bias is introduced by excluding this subset).

Patients who die post-discharge, experience loss of capacity in the data collection period, are lost to follow-up or have progressed to palliative care will be considered high-level drinking (composite outcome). The hypothetical strategy 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. In the case where a participant is hospitalised during the period covered by the Timeline Follow Back (TLFB) assessment (i.e. up to 28 days prior to 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. The

principle of using available data will apply more generally where data is not complete for 28 days for reasons other than hospitalisation.

The primary endpoint is therefore alive with abstinence or low risk level drinking, no loss of capacity or transition to palliative care in those who do not die before initial discharge, and in the absence of hospitalisation at 180 days.

Other reasons for missing primary outcome data include withdrawal (by participant or clinician) or unusable data (i.e. to calculate number of units from information provided). Methods for imputing these data will be used for the primary analysis.

There are 4 pre-planned subgroup analyses: severity of liver disease (Child–Pugh score: non-cirrhotic, A, B and C), chronic pain score (yes/no) and digital literacy and patient empowerment score (continuous).

There is potential for some of the deaths to be unrelated to liver disease; therefore, a secondary analysis will be conducted considering those that die due to liver disease as high-level of drinking and those that die due to non-liver disease causes. We will use the same strategy as hospitalisation (i.e. we will consider the hypothetical scenario where death does not occur). An independent review of the deaths will be conducted at the end of the trial to classify deaths into liver disease related and non-liver disease related. Imputation methods will be used for those that have missing data due to death from non-liver related causes.

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.

Integrated health economic evaluation

The cost-effectiveness analysis (CEA) will take a health and personal health services perspective as recommended by NICE [18]. The CEA will use patient-level healthcare resource use and outcome data collected as a part of the trial through trial case report forms and follow-up clinic visits and patient questionnaires. An analysis plan for the health economic outcomes will be written and integrated with the SAP. Data on the use of NHS resources at baseline, 90 and 180 days post-randomisation will be collected. Resource use data will be valued using appropriate unit costs to calculate total costs per patient for up to 180 days since randomisation. HRQoL data will be collected at baseline, 90 days and 180 days using EQ-5D-5L, which 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. Missing data in costs and outcomes (HRQoL, survival) will be imputed using the Multiple Imputation method.

Baseline measures are conducted at a single outpatient visit (for outpatients), or at any time between consent and discharge (for inpatients).

Ethics and dissemination

The study has ethics approval in the UK (21/NW/0177). Dissemination will include publication of the early development and preparation work, and then papers on the clinical and economic implications.

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 will be created (Table 2).

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.

Once the study has completed, data may be requested from the Data Access Committee at SCTU. 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 3 months after the 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.

Discussion

AlcoChange was designed as a pragmatic trial to assess a new digital therapeutic which could plausibly be added to standard care in the management of patients with alcohol-related liver disease and ongoing alcohol use. The trial is also notable, as it is one of the largest randomised controlled trials of a digital therapeutic, to-date, in the UK.

Our initial approach was to design it as a stepped wedge trial for three reasons. Firstly, there was concern

Table 2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Adults aged 18 years or older with a diagnosis consistent with ArLD. This may include (a) established cirrhosis, (b) liver fibrosis or steatohepatitis without established fibrosis (assessed by non-invasive means e.g. transient elastography), (c) alcoholic hepatitis† within 6 weeks, (d) established ARLD in the opinion of the investigator 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 (iphones 8 or android OS 8 or higher) 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 (> 50 g/day, for at least 6 months) • Serum bilirubin > 51 µmol/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	1. Taking part in another interventional study 2. Referred for end-of-life palliative care 3. Referred for in-patient alcohol rehabilitation in a tertiary facility 4. If recruited as an in-patient, severe liver failure during inpatient stay (acute-on-chronic liver failure grades 2 or 3) 5. Multiple (> 6) alcohol-related hospitalisations during the preceding 2 years

about potential contamination, since staff who were exposed to the AlcoChange intervention might change their behaviours and thus alter treatment as usual. This suggested that a cluster design of some form would be appropriate. Secondly, part of the goal of NIHR i4i as a funder is to learn about implementation of the intervention, with a view to facilitating future commercialisation should it be shown to be effective. To achieve this, we wanted as many sites as possible to have experience with the intervention. With a conventional cluster design, only half the sites would have intervention experience; using a stepped-wedge design, all sites would have had experience of the intervention by the end of the study. Thirdly, this design was thought to offer some logistic benefits in trial delivery. With centres commencing intervention delivery in sequence, they could be trained in sequence, and requirements for device delivery to centres would be clearer.

However, the design of the study was changed due to challenges imposed by the Covid-19 pandemic. The set-up of the trial was initiated in 2021, during a time in which the NHS research governance processes were, appropriately, prioritising Covid-related studies. Consequently, it became clear that the original stepped-wedge design would not be feasible, since it relied on having 18 sites ready to start simultaneously. In other words, the date of trial initiation would be governed by the speed of the slowest site, and with the superimposed pressures this could have delayed study start by over a year. Fortunately, during our initial development work, it became clear that initial concerns regarding staff contamination by exposure to the novel intervention were unfounded. Without being able to provide patients access to the Alcochange device and the website behind it, staff behaviours and the patient experience were unchanged. Therefore, we were able to refashion the effectiveness portion of the study as an individually randomised trial, which allowed the study to open with 6 sites, rising to 18 over the following 6 months.

Our primary endpoint is reduction in alcohol consumption to government recommended safe levels. The overarching goal of treatment in ARLD is to achieve complete abstinence, which has been shown to improve prognosis across all stages of the disease [19]. However, reduction of alcohol use to low-risk levels is associated with mortality benefit in ARLD, albeit less effective than complete abstinence [20]. Additionally, there is evidence to suggest a staged approach to reducing drinking may be more acceptable to patients with ARLD, consequently enhancing engagement with treatment [21, 22]. Therefore, a composite of complete abstinence or reduction to low-risk drinking at 180 days was chosen as a pragmatic endpoint for this trial. However, all patient-facing messaging within the study consistently focusses on complete abstinence as the treatment goal.

A major part of the development work for this trial was refining the tool for capture of self-reported alcohol intake. The TLFB is a widely validated method of assessing alcohol use; it is considered the gold standard for clinical trials and is accepted by regulatory bodies. However, the available training materials for TLFB were not culturally appropriate for a UK population, and new materials have been developed. Urinary biochemical markers of recent alcohol use are increasingly

being used, but do not typically provide information on alcohol use beyond 3–5 days. Additionally, the interpretation of results would only assist with a binary endpoint of complete abstinence, rather than low-risk drinking. In this trial, urinary ethyl glucuronide is being measured as a tertiary, exploratory endpoint, and will be analysed to determine concordance with TLFB data over the preceding 3–5 days.

Finally, an outstanding point of concern for this trial, and all hepatology trials in the UK with a 'usual care' arm, remains a standardised level of usual care. From the point of view of alcohol services, we have predominantly selected sites with an ACT for this trial, and we aim to capture data regarding local provision of additional alcohol services provided by the third sector (e.g. charity services, voluntary groups). The overarching point regarding standardised care for liver patients in the UK remains an issue for randomised trials with a 'usual care' arm. This has been discussed in several fora, such as the recently developed UK-CLIF cirrhosis research network, and the imminent publication of quality standards for the provision of inpatient and outpatient care in cirrhosis will hopefully have an impact in this area.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-09005-3.

Supplementary Material 1.

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Authors' contributions
GM and AC developed the initial protocol. All authors have been involved with protocol redesign. AC wrote the first draft of this paper, drawing on the main protocol document. All authors have reviewed, commented on, and approved this paper.

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Data Availability
Not applicable.

Declarations

Competing interests
Andrew Cook declares no competing interest.
Sean Ewings declares no competing interest.
Megan Lawrence declares no competing interest.
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Gautam Mehta owns shares in Yaqrit Ltd and Hepyx Ltd, which are involved in the development of therapies for advanced liver disease.

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References

1. Williams R, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. Lancet. 2014;384(9958):1953–97.
2. National Confidential Enquiry into Patient Outcome and Death, Measuring the units: a review of patients who died with alcohol related liver disease. 2013.
3. Office for National Statistics, Alcohol-specific deaths in the UK: registered in 2017. 2018.
4. Diehl AM. Alcoholic liver disease: natural history. Liver Transpl Surg. 1997;3(3):206–11.
5. Kaner EF, et al. Effectiveness of brief alcohol interventions in primary care populations. Cochrane Database Syst Rev. 2018;2:CD004148.
6. Kaner EF, et al. The effectiveness of brief alcohol interventions in primary care settings: a systematic review. Drug Alcohol Rev. 2009;28(3):301–23.
7. Preben Bendtsen PA, Wojnar M, Newbury-Birch D, Müssener U, Colom J, Karlsson N, et al. Professional's attitudes do not influence screening and brief interventions rates for hazardous and harmful drinkers: results from ODHIN Study. Alcohol Alcohol. 2015.
8. Free C, et al. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. Lancet. 2011;378(9785):49–55.
9. Mehta G, et al. AlcoChange: a digital therapeutic for patients with alcohol-related liver disease. JHEP Rep. 2024;6(4): 100993.
10. Mehta Gautam KM. AlcoChange – a smartphone tool to reduce alcohol use and admissions in alcoholic liver disease. London: Royal Free London NHS Trust; 2017.
11. Reed JE, et al. Successful healthcare improvements from translating evidence in complex systems (SHIFT-Evidence): simple rules to guide practice and research. Int J Qual Health Care. 2019;31(3):238–44.
12. Bamber J. Quality imprvement in surgery - basic principles 2021.
13. Davidoff F, et al. Demystifying theory and its use in improvement. BMJ Qual Saf. 2015;24(3):228–38.
14. Crombie IK, et al. Texting to Reduce Alcohol Misuse (TRAM): main findings from a randomized controlled trial of a text message intervention to reduce binge drinking among disadvantaged men. Addiction. 2018.
15. FormsVision BV. Alea tools for clinical trials. [Website] 2023 [cited 2023 1st August 2023]; Available from: https://www.aleaclinical.eu.
16. Cobain K, et al. Brief interventions in dependent drinkers: a comparative prospective analysis in two hospitals. Alcohol Alcohol. 2011;46(4):434–40.
17. Schulz KF, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340: c332.
18. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. London: National Institute for Health and Care Excellence; 2022.
19. Hofer BS, et al. Alcohol abstinence improves prognosis across all stages of portal hypertension in alcohol-related cirrhosis. Clin Gastroenterol Hepatol. 2023;21(9):2308–2317 e7.

20. Atkinson SR, et al. People who survive an episode of severe alcoholic hepatitis should be advised to maintain total abstinence from alcohol. Hepatology. 2018;67(6):2479–80.
21. Adamson SJ, et al. Initial preference for drinking goal in the treatment of alcohol problems: II. Treatment outcomes. Alcohol Alcohol. 2010;45(2):136–42.
22. Heather N, et al. Initial preference for drinking goal in the treatment of alcohol problems: I. baseline differences between abstinence and non-abstinence groups. Alcohol Alcohol. 2010;45(2):128–35.

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