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Mental Imagery to Reduce Alcohol-related harm in patients with alcohol dependence and alcohol-related liver damaGE: the MIRAGE pilot trial protocol

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ABSTRACT (300 words)

Introduction

In the UK, alcohol use is the main driver of chronic liver disease and each year results in over one million unplanned hospital admissions and over 25,000 deaths from alcohol-related liver disease (ArLD). The only effective treatment to prevent progression of liver damage is reducing or ceasing alcohol consumption. Psychological and pharmacological therapies for alcohol misuse are ineffective in patients with ArLD. Functional Imagery Training (FIT) is a novel psychological therapy that builds on motivational interviewing techniques with multi-sensory imagery. This pilot trial aims to test the feasibility of training alcohol liaison nurses to deliver FIT therapy and of recruiting and retaining patients with ArLD and alcohol dependence to a randomised trial of FIT and treatment as usual (TAU) versus TAU alone.

Methods and analysis

This is a randomised pilot trial of FIT and TAU versus TAU alone in 90 patients admitted to one of four UK centres with ArLD and alcohol dependence. The primary objectives are to estimate rates of screening, recruitment, randomisation, retention, adherence to FIT/TAU and a preliminary assessment of the FIT intervention in the ArLD population. Data from the pilot study will be used to finalise the design of a definitive randomised controlled trial to assess effectiveness and cost-effectiveness of FIT. The proposed primary outcome measure for the definitive trial is self-reported alcohol use assessed using Timeline Follow-back.

Ethics and dissemination

Research ethics approval was given by the Yorkshire and Humber – Leeds Bradford Research Ethics Committee (ref: 21/YH/0044). Eligible patients will be approached and written informed consent obtained prior to participation. Results will be disseminated through peer-reviewed open access

journals, international conferences and a lay summary published on the Trials Unit website and made available to patient groups.

Trial registration number: ISRCTN41353774).

Keywords

Hepatology

Health Economics

Substance Misuse

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study will examine the feasibility of alcohol liaison nurses delivering FIT, in addition to usual care, in an NHS setting.
- An economic evaluation framework will be tested to ensure the feasibility of estimating cost-effectiveness in the definitive trial.
- This is a pilot study and therefore is not powered to detect differences in clinically relevant outcomes.
- This pilot study is being conducted with a 180-day follow-up thus limiting the opportunity for obtaining longer-term outcomes.

INTRODUCTION

Alcohol use is the third leading cause of premature death in the UK[1] and is the main driver of chronic liver disease. Alcohol was involved in over 1.1 million unplanned hospital admissions in 2017/8, of which 63,000 were due to alcohol-related liver disease (ArLD), and led to 25,000 deaths.[2] Due to increased alcohol consumption among high-risk drinkers during the COVID-19 pandemic, the number of alcohol-related hospital admissions increased by 3.2% and the number of ArLD deaths by 21% compared to the previous year.[3] Alcohol-related healthcare costs £3.5 billion to the NHS directly and up to £52 billion to the UK economy annually.[4]

ArLD is caused by long-term alcohol consumption, usually with physiological and psychological dependence, characterised by liver damage (fibrosis) leading to cirrhosis, which impacts patients' quality of life[5] (QoL) and survival.[6] Alcohol dependence is characterised by craving, tolerance, a preoccupation with alcohol and continued drinking despite harmful consequences.[7] The only effective treatment to prevent progression of liver damage is reducing or ceasing alcohol consumption.[6] Patients who continue to drink heavily develop progressive liver damage[8] and have a higher risk of death than patients who abstain from alcohol.[9] In a subgroup of ArLD patients with alcoholic hepatitis, an acute inflammatory liver injury, two-thirds of patients relapse to alcohol consumption within six months of hospital discharge and have a three- to four-fold risk of death within one year compared to those who maintain abstinence from alcohol.[10 11] Few interventional trials have been conducted in this patient population and none are currently registered on clinicaltrials.gov.[12]

Treatment as usual (TAU) for this patient group is a brief intervention, a form of motivational interviewing (MI), conducted by a trained health professional, usually an Alcohol Liaison Nurse (ALN), during the inpatient stay, lasting less than 20 minutes and signposting patients to community

services, as recommended by the National Institute for Health and Care Excellence (NICE).[7] However, early relapse to drinking alcohol after hospital admission remains a challenge[10] and pharmacological treatments are not yet an option. Acamprosate, disulfiram, naltrexone and nalmefene are licenced for the treatment of alcohol dependence but are unsuitable for patients with chronic liver disease due to their altered drug metabolism. Three randomised controlled trials (RCTs) of baclofen in patients with chronic liver disease have reported conflicting results.[13-15] Uncertainty remains over efficacy, tolerability and dosing of baclofen for patients with liver disease.

Reviews of MI delivered to heavy drinkers admitted to hospital suggest significant reductions in alcohol consumption and deaths but confound TAU (a single brief session) with multi-session MI[16]. Trials of multi-session MI report favourable 1-3 year outcomes[17 18] but have intervened in outpatient rather than inpatient settings. In outpatients with ArLD, MI was effective in inducing abstinence but further studies are required to evaluate its use in maintaining abstinence.[19] There is a need for a psychological intervention that effectively motivates sustained abstinence. Ideally, this intervention would capitalise on receptiveness to change immediately after unplanned hospital admission, as TAU does, and extend support beyond discharge, as multi-session MI does. It should also incorporate mental imagery to amplify the effects of MI[20] and teach patients how to use imagery and MI techniques themselves to extend the duration of benefits.

Functional Imagery Training (FIT) is a new treatment that combines MI with evidence-based imagery training to further strengthen motivation, combat craving, and train self-management skills.[20 21] In a typical FIT session, individuals are encouraged to create multi-sensory mental images of achieving their goal, taking the first steps needed to work towards their goal, and using previously successful strategies to work around potential obstacles to their goal. Having generated these component images, the individual puts them together into a personal mental 'movie' in which they start working

successfully on their plan. The individual is encouraged to practice this imagery frequently by pairing it with a routine 'reminder' behaviour like hand washing.

FIT has a strong scientific basis, including research on alcohol use and alcohol reduction. Substantial research shows that more vivid imagery of seeing, tasting, smelling and swallowing alcohol accompanies stronger alcohol cravings[22-24] and consumption.[25] Imagery of why (incentives) and how (self-efficacy) the person will change also accompanies motivation for functional behaviour change goals, including alcohol reduction.[26 27] Benefits of FIT for behaviour change have been shown in other contexts, including motivating dietary change and increasing athletes' resilience[21 28 29] and motivation.[30] A recent RCT showed benefits of FIT over MI for weight management over 12 months. This trial comprised 4 hours of intervention, delivered in 8 sessions over 6 months, followed by 6 months unsupported. Participants who received FIT lost more weight initially and continued losing weight in the 6 months after the intervention ended. An RCT of FIT versus MI for alcohol reduction is ongoing in Australia (ACTRN12616000480482). That trial is recruiting self-referred participants with alcohol dependence in a community setting and delivering interventions by telephone. There remains a need to test this intervention in patients with ArLD ill enough to be hospitalised.

A definitive trial would aim to determine the clinical and cost-effectiveness of the addition of FIT to TAU in reducing alcohol-related harm over 6 months in patients with ArLD and alcohol dependence. However, before designing and running such a definitive trial, we need to find out whether patients with ArLD are interested and willing to take part in randomised trials and how well ALNs can deliver FIT. In addition, we need to collect information to i) finalise the choice of outcome measures; ii) determine the cost-effectiveness framework; iii) estimate the effect size of FIT on alcohol consumption and iv) inform how many patients we would need to recruit in a definitive trial.

METHODS AND ANALYSIS

This protocol is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance for protocols of clinical trials.[31] Appendix 1 contains the study protocol v3.1 dated 3.2.22.

Pilot trial primary objectives

To conduct a randomised pilot trial of FIT and TAU versus TAU alone to:

1. Estimate rates of screening, recruitment, randomisation, retention, adherence to FIT/TAU and possible contamination of TAU where ALNs are trained to deliver both FIT and TAU.
2. Allow a preliminary assessment of FIT intervention in the ArLD population.

Pilot trial secondary objectives

1. To estimate the resource use and costs associated with delivery of FIT and TAU, and to pilot methods for the cost-effectiveness framework in a full trial.
2. To identify if there is a need to improve FIT training and delivery by ALNs within the NHS and if so, methods for improvement.

Study setting

This pilot study is set in the acute NHS sector in four NHS Trusts in England (University Hospitals Plymouth NHS Trust, University Hospitals of Bristol and Weston NHS Foundation Trust, Leeds Teaching Hospitals NHS Trust and Royal Devon and Exeter NHS Foundation Trust).

Patient population

This includes all patients with ArLD and alcohol dependence admitted to hospital aged ≥18 years with high-risk alcohol consumption and Alcohol Use Disorder Identification Test (AUDIT) > 15. See Table 1 for eligibility criteria.

Table 1. Patient eligibility criteria

Inclusion Criteria	Exclusion Criteria
Patients must satisfy all of the following criteria to be enrolled in the study:	**Patients who meet any of the following criteria will be excluded from study participation:**
Adult patients ≥18 years	Any condition with an estimated life expectancy of less than 6 months
Able and willing to provide written informed consent	Patients participating in concurrent interventional research
Clinical diagnosis of ArLD by at least one of the following methods • radiological appearance of fatty infiltration of the liver or cirrhosis • histological findings of cirrhosis or alcoholic steatohepatitis • signs consistent with chronic liver disease on physical examination	Patients who have significant difficulties in adequate understanding of English such that they are unable to benefit from the trial intervention or sufficiently understand the trial documentation
High risk alcohol consumption (>50 units/week for males and >35 units/week for females) within 4 weeks prior to hospital admission	Prisoners
Alcohol Use Disorder Identification Test (AUDIT) score[32] >15 during current hospital admission	Patients who do not have access to a telephone so would be unable to participant in FIT sessions
Diagnosis of alcohol dependence documented by clinician in medical records. This should be with reference to the ICD-10[33] meeting at least three of the following conditions: • strong desire or sense of compulsion to take alcohol • difficulties in controlling alcohol-consuming behaviour in terms of its onset, termination, or levels of use • a physiological withdrawal state when alcohol use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome; or use of alcohol with the intention of relieving or avoiding withdrawal symptoms • evidence of tolerance, such that increased doses of alcohol are required in order to achieve effects originally produced by lower doses • progressive neglect of alternative pleasures or interests because of alcohol use, increased amount of time necessary to obtain or consume alcohol or to recover from its effects • persisting with alcohol use despite clear evidence of overtly harmful consequences.	

Consent

The site Principal Investigator (PI) or an authorised delegate, trained in the relevant principles of Good Clinical Practice and the requirements of the trial protocol, will obtain written informed consent prior to the collection of any trial data. See appendix 2 for the Informed Consent Form. At the start of each FIT session and trial follow-up visit, the practitioner will assess mental capacity, check for alcohol intoxication by participant self-report and confirm willingness to continue the visit. If the participant lacks capacity due to alcohol intoxication, the visit will be rescheduled. If a participant lacks capacity for any other reason, they will be withdrawn from the trial.

Outcome measures

Pilot trial outcome measures

- Recruitment rate during the total 10 month recruitment period (overall and by site)
- Retention rate at 90 and 180 days (overall and by site)
- Fidelity of delivery of FIT and TAU (further details below)
- Intervention engagement – number of successful FIT phone calls and visits (where a session of FIT has been received)
- Completeness of data collection.

Participant reported and other clinical outcomes

The proposed primary outcome for a future definitive trial is change in self-reported alcohol use (grams of pure alcohol/week) between baseline and 180 days post-baseline. Alcohol use will be assessed using the timeline follow-back technique[34], which is used to determine an individual's alcohol use over the 7 days immediately prior to their hospital admission (baseline) and at 28, 90 and 180 days post-baseline.

Alcohol use is challenging to measure objectively. Direct or indirect alcohol biomarkers are inaccurate or untested in patients with liver disease.[35] The timeline follow-back method is a systematic tool to record alcohol use and avoids the reactivity of self-monitoring[36] and has been used as a primary outcome measure in RCTs in people with alcohol dependence.[37]

Proposed participant reported secondary outcomes for a future definitive trial completed at baseline and follow-up (see Table 2 for assessment time points), are:

- Severity of Alcohol Dependence Questionnaire (SADQ), a validated 20 item questionnaire, which correlates with the degree of alcohol dependence[38]
- EQ-5D-5L questionnaire to measure health-related quality of life
- Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)[39] to measure mental wellbeing. In the pilot study the full version will be used, which will also allow calculation of the short form version (SWEMWBS)[40], to inform which version is most appropriate for the definitive trial
- Health, social care and wider care services utilisation will be determined using a resource use questionnaire
- Self-reported re-hospitalisation within 180 days post-baseline or, if unobtainable, determined using hospital records at participating sites
- Self-reported time to relapse to regular alcohol use (5 or more drinking days per week or 5 or more units in a single day).[41]

Exploratory biochemistry outcomes

At 180 days post-baseline, we will measure:

- Alcohol metabolites using urinary biomarkers (ethyl glucuronide/sulphate) that provide a highly sensitive and specific objective quantitative measure of alcohol consumption within the preceding 72 hours.[42]

Table 2. Summary of outcome measures

	Baseline	Day 28 (±7)	Day 90 (±7)	Day 180 (±14)
Current alcohol use[†]	X	X	X	X
SADQ score	X	X	X	X
Re-hospitalisation rate		X	X	X
Self-reported time to relapse		X	X	X
WEMWBS Questionnaire[‡]	X	X	X	X
EQ-5D-5L Questionnaire	X	X	X	X
Health and Social Care resource utilisation	X		X	X
Urine sample for alcohol metabolites				X

[†]Self-reported alcohol use (units of alcohol) over a period of 7 days obtained using the timeline follow-back method. At baseline, this covers the seven days prior to hospital admission. Post-allocation, this covers the seven days prior to the data collection timepoint.. [‡]including SWEMWBS

Trial design

Multicentre randomised controlled pilot trial of FIT+TAU (intervention group) vs TAU alone (control group).

Randomisation

Participants are allocated to receive TAU or TAU+FIT, in a 1:1 ratio, using random permuted blocks, stratified by recruiting site and the participant's baseline SADQ total score, dichotomised as ≤30 (moderate) or >30 (severe)[38]. Web-based randomisation is managed by the Peninsula Clinical Trials Unit (PenCTU).

Blinding

This trial is non-blinded to ALNs and participants, as it is not possible to conceal the active FIT intervention from them. The outcome assessors (i.e. research team members conducting research visits) and the trial statistician undertaking the analyses are blinded to treatment allocation.

TAU

All participants receive TAU which comprises one brief MI-based session given in hospital by an ALN Due to local hospital practices, participants may have received TAU prior to being approached about this study, prior to giving informed consent to participate, or prior to completing the trial baseline measures and being randomised.

Intervention

A manualised FIT intervention will be delivered by a member of the site's alcohol services team and comprises one session given face-to-face to participants before discharge from hospital, a second session given, if possible, face-to-face to participants in an outpatient clinic or via telephone. A further seven sessions are then delivered by telephone over a period of 6 months (figure 1).

FIT treatment sessions

Session 1

This inpatient face-to-face session takes place at any time from randomisation to date of hospital discharge. This session lasts less than 60 minutes and introduces mental imagery as a skill people can use to help them achieve their goals. Mental imagery is used to strengthen desire for change; to mentally rehearse a simple plan for the next few days and strengthen commitment to it; to explore ways to overcome barriers; to strengthen confidence by replaying past successes and strategies.

Session 2

This session takes place either face-to-face in the hospital outpatient department or by telephone within 10 days of discharge from hospital. The session lasts less than 45 minutes and is included to support motivation early after hospital discharge.

Session 3

This session takes place by telephone at Day 14 (±4 days) post-hospital discharge and lasts less than 30 minutes. Booster calls affirm progress, develop imagery about recent successes, problem solutions, new goals or behaviours, and encourage practice.

Sessions 4-9

These six sessions take place by telephone at Days 28, 42, 56, 90, 120 and 180 (all ±7 days) post-hospital discharge. All sessions last less than 15 minutes.

Intervention fidelity assessment

Where participants consent, their first and second FIT session will be audio recorded for fidelity checking and assessment of contamination. A trained FIT practitioner will check each ALN's fidelity early in the trial using a dedicated fidelity assessment tool previously developed, the FIT-QC 2.0[43], and give individual feedback on their first session. The FIT-QC contains 9 items covering motivational interviewing elements (building positive expectancies of change, collaboration, empathic reflection), functional imagery (delivering structured session, creating opportunity for imagery, giving individually tailored support for imagery generation, refining quality and content of imagery, amplifying emotional impact of imagery) and training (developing skills of self-motivation using imagery). Items are scored between 0 and 4 where 0 means that the target behaviour or characteristic is absent or used poorly and 4 means it is consistently displayed and correctly used. A rating of 2 represents satisfactory performance on the item. Across the FIT-QC, a mean score of 0 means that the interaction did not meet the aims of FIT, 2 represents a satisfactory interaction where the different elements were usually delivered correctly and weaknesses were judged unlikely to have undermined rapport or motivation. A mean of 4 represents a proficient interaction where the differently elements are used correctly and tailored sensitively to the person's responses to maximise their motivational impact.

In addition, an experienced FIT practitioner outside the project team will use the same scale to rate two FIT sessions from the first five patients and two from the last five patients for each ALN, to determine the standard of FIT delivery across the study. ALNs will regularly self-assess potential contamination by recording whether they mentioned imagery (mild contamination) or guided imagery (strong contamination) during TAU sessions.

Trial follow-up visits

All participants will be scheduled for telephone follow-up at 28 (±7) and 90 (±7) days and face-to-face follow-up at 180 (±14) days post-baseline. **Error! Reference source not found.** shows participants' progression through the study.

Participant retention strategy

To maximise retention at FIT sessions and/or trial follow-up visits, the site team will collect a secondary contact name and phone number. The site team will attempt to contact the participant on up to three occasions by phone. If contact has not been made, the secondary contact number will be called. If still not contactable, no further attempts will be made until their next scheduled FIT session or follow-up visit. The participant's GP may be contacted by a member of the site team at this point to check their status.

To incentivise retention, participants will receive a single payment of £20 (as a cash payment or as a voucher) after completion of the final trial visit.

Study management

The study sponsor organisation is the University Hospitals Plymouth NHS Trust, Derriford, Plymouth PL6 5FP. Day to day trial management is administered through the UKCRC-registered Peninsula Clinical Trials Unit (PenCTU) at the University of Plymouth. PenCTU conducts central and site monitoring in accordance with a risk-based monitoring plan and the study sponsor may audit trial conduct as deemed appropriate.

The Trial Management Group (TMG) meets monthly to monitor the progress of the trial, and to address any issues that may arise. The Trial Steering Committee (TSC), with an independent chair, clinician, statistician and two other patient members, meets twice a year to oversee the conduct of the trial, to monitor safety and ethical issues, including any participant drop-outs and overall data completeness. A Data Monitoring Committee was not considered necessary for this pilot trial but will be convened for a definitive trial.

Data management and confidentiality

Research teams at all sites will ensure that participants' anonymity is maintained on all documents. Data are collected and stored in accordance with the Data Protection legislation which includes the UK Data Protection Act 2018 and the General Data Protection Regulation, 2018. Each participant has been allocated a unique study number and is identified in all study-related documentation by their study number and initials.

A web-based application developed by PenCTU is used for trial management and for recording participant data. This consists of a bespoke system for screening, randomisation and management of participants integrated with an electronic case report form (eCRF) built in REDCap Cloud. Anonymised data will be available upon request to the chief investigator or sponsor. Anonymised data will be exported to the trial statistician.

Sample Size Calculation

We estimate that across all sites, 32 potentially eligible ArLD patients are admitted per month. Allowing for staggered site set-up and an 11-month recruitment window, we anticipate screening ~180 patients; with a conservative recruitment rate of 50% of those screened, our total recruitment target is 90 participants. This will allow estimation of the overall retention rate with a 95% confidence interval (CI) with precision of at least ±11%. Assuming a non-differential retention rate of 75% at the 180-day follow-up (the anticipated primary endpoint for a definitive trial), indicates primary outcome data will be available from a minimum of 33 participants within each allocated group.

Analysis Populations

Primary analysis, in the form of summary statistics, will be undertaken on a modified Intention To Treat (mITT) basis, where participants are analysed according to their allocated group, regardless of adherence to the protocol or lack of participation or completion if allocated to the intervention group. Missing outcome data will not be imputed in this pilot study, except for validated outcomes where there is a published method for imputing missing items. The safety population will include all participants who consent to partake in the study, with safety data collected from the time of recruitment until a participant completes or withdraws from the study.

Statistical Significance Levels

As this is a pilot trial, no inferential between-group hypothesis testing will be undertaken. Feasibility outcomes, such as recruitment rates, will be presented with two-sided 95% confidence intervals. Between-group differences for proposed trial outcomes will be summarised descriptively and presented with two-sided 75%, 85% and 95% confidence intervals.[44] Estimates that may be used for

future sample size calculations (e.g. standard deviation of proposed primary outcome) may be presented with alternative confidence intervals. A detailed statistical analysis plan has been developed and will be approved by an independent statistician prior to database lock and made publicly available at https://pearl.plymouth.ac.uk.

Safety reporting

Safety and tolerability of the trial treatment is monitored throughout the study by means of follow-up review of all participants. All serious adverse events (SAEs) are recorded and reported, whether they are deemed related to the trial treatment or not. Quarterly summaries of all SAEs are provided to the TSC and study sponsor. Any potential Sudden Unexpected Serious Adverse Reaction (SUSAR) will be reported immediately to the sponsor who will report onwards as necessary.

ECONOMIC EVALUATION

This pilot study will test the methods for a subsequent, policy-relevant, cost-effectiveness analysis (CEA) of FIT and TAU, compared to TAU. This future economic evaluation will be undertaken alongside the definitive RCT and will establish the resources required to provide the FIT intervention, estimate intervention costs, and conduct a full CEA. The intervention costing and CEA, based on within-trial data collection, will be undertaken against a primary perspective of the NHS/Social Care, with participant and broader societal perspectives considered in sensitivity analyses. The economic evaluation will follow the internationally recognised Consolidated Health Economic Evaluation Reporting Standards (CHEERs) guidelines for reporting cost-effectiveness studies.[45] A Health Economics Analysis Plan (HEAP) will be developed and agreed prior to database lock.

Intervention costing

As part of this pilot study, the resources required to deliver the FIT intervention will be assessed via participant-level case-records, and discussion with the intervention developers and providers. ALNs' time will be documented in terms of per-participant contact and non-contact time. Training and supervision resources will also be documented.

Nationally recognised UK unit costs for health and social care services[46] will be applied to this resource use data. The mean cost per participant of the intervention will be estimated.

Health, social and wider care resource use

A self-report bespoke resource use questionnaire has been developed in collaboration with the study's PPI group, informed by the Database of Instruments for Resource Use Measurement (DIRUM)[47] and the core items for a standardised resource use measure.[48]

Quality-adjusted life-years (QALYs)

Participants will complete the EQ-5D-5L[49] at baseline and at Day 28, Day 90 and Day 180 follow-ups. The EQ-5D is a generic measure of health-related quality of life. In accordance with the current 'position statement' of NICE,[50] the 'approved' cross-walk algorithm will be used to map EQ-5D-5L responses to the EQ-5D-3L health state utility value set to estimate participant-level QALY weights.[51] [52]

QUALITATIVE STUDY

Decliner and participant interviews

Short telephone interviews will be conducted with patients who were eligible but declined to take part (n=8) to identify their reasons for this.

After the 180 day follow-up window has been reached, participants who agreed to be contacted will be interviewed by telephone to inform our understanding of acceptability and feasibility of trial methods (control n=8, intervention n=12). There will be a focus on study materials, motivation for taking part, understanding and experience of randomisation and, additionally, for intervention participants, their engagement with FIT.

Informed consent will be obtained either in writing or by audio recording of verbal consent. Participants will be sampled equally from each site and those in the intervention arm will be balanced according to engagement in FIT treatment (those who completed the ≥2 FIT sessions versus those that did not).

Research nurses

Research nurses will be invited to virtual meetings monthly during the early recruitment and follow-up phase). They will discuss recruitment and retention rates, including any identified barriers or challenges, and discuss interview data from patients who declined to take part to inform strategies to enhance both. Detailed notes will be made of the meetings, including any proposed changes to recruitment and retention strategies and impact.

ALNs

All ALNs participating in the study will be invited to take part in two 60-minute virtual focus groups, one early and one later in the intervention delivery phase of the trial. Informed consent will be obtained either in writing or by audio recording of verbal consent. The objectives of these discussions are:

- To assess the acceptability and utility of FIT training, manual and supervision
- To identify barriers and facilitators to FIT delivery
- To identify methods to improve delivery and implementation within the NHS

Qualitative analysis

Telephone interviews will be recorded and transcribed verbatim and uploaded to NVivo 12 software for organisation and analysis. Data will be analysed using thematic analysis adopting Braun and Clarke's six-phase process[53] of (i) data familiarisation; (ii) coding; (iii) generation of initial themes; (iv) reviewing themes; (v) defining and naming themes and (vi) writing up to identify patterns of meaning within the data sources.

PUBLIC AND PATIENT INVOLVEMENT

Public and patient involvement (PPI) representatives are actively involved in the study with two representatives invited to join the trial management group (TMG) and trial steering committee (TSC) respectively. These patient representatives form an advisory group led by a PPI coordinator and advised on protocol development and study design. They helped to tailor the FIT manual to the ArLD population and advised on topics guides to be used in the qualitative study. ArLD patients and the PPI group review all patient-facing written material and will be involved in the dissemination of results via their support and local community groups.

TRIAL PROGRESS

Recruitment of the first participant occurred on 21/04/2021. The recruitment period ended on 28/02/2022 and the final follow-up visit will be completed by 31/08/2022 +/- 14 days.

ETHICS AND DISSEMINATION

The Chief Investigator has obtained approval from the Health Research Authority (HRA) and Yorkshire and Humber – Bradford Leeds Research Ethics Committee (REC ref: 21/YH/0044). The Chief Investigator, with oversight from the study sponsor and independent Trial Steering Committee, will ensure that this study is conducted in full conformity with relevant regulations and with the UK Policy Framework for Health and Social Care Research (2017), which have their basis in the Declaration of Helsinki. All participants will provide written informed consent (see appendix 2). The study is registered with the ISRCTN Registry (ISRCTN41353774). It has been adopted onto the Clinical Research Network portfolio by the National Institute for Health Research.

The trial will be reported in accordance with guidance from the CONSORT extension for pilot and feasibility trials[54] and submitted to a peer-reviewed medical journal as open access. Plain language summaries will be disseminated to participants and patient groups and will be available on the PenCTU website.

DISCUSSION

MIRAGE is a UK multicentre pilot RCT that aims to assess the feasibility of delivering a novel psychological therapy (FIT) to patients with alcohol dependence and ArLD, commenced in an in-patient setting. Since this intervention has never before been delivered to inpatients with ArLD, we need to determine whether patients would be willing to be recruited, randomised and followed-up in a trial of FIT and TAU versus TAU alone. Additionally, as FIT has not previously been delivered by ALNs, we need to determine the practicalities of training these healthcare professionals and to assess the fidelity of the intervention they provide.

As well as assessing key pilot trial outcomes, we will evaluate the proposed primary outcome for the definitive trial of change in self-reported alcohol use in grams of pure alcohol per week from baseline to day 180. This has been selected as ongoing alcohol use in this group of patients is associated with greater risk of disease progression[55] and mortality in a dose dependent manner.[10]

As a pilot trial, it is not powered to detect clinically relevant differences in outcomes. Furthermore, with limited follow-up of 180 days, it will not be able to determine differences in longer term outcomes. However, both of these limitations can be addressed in a definitive RCT. All treatment provided in the trial (TAU and FIT) are delivered by ALNs and there is therefore a risk of contamination of TAU with imagery techniques used in FIT. To address this, ALNs will regularly report whether they mentioned imagery or used guided imagery during TAU sessions.

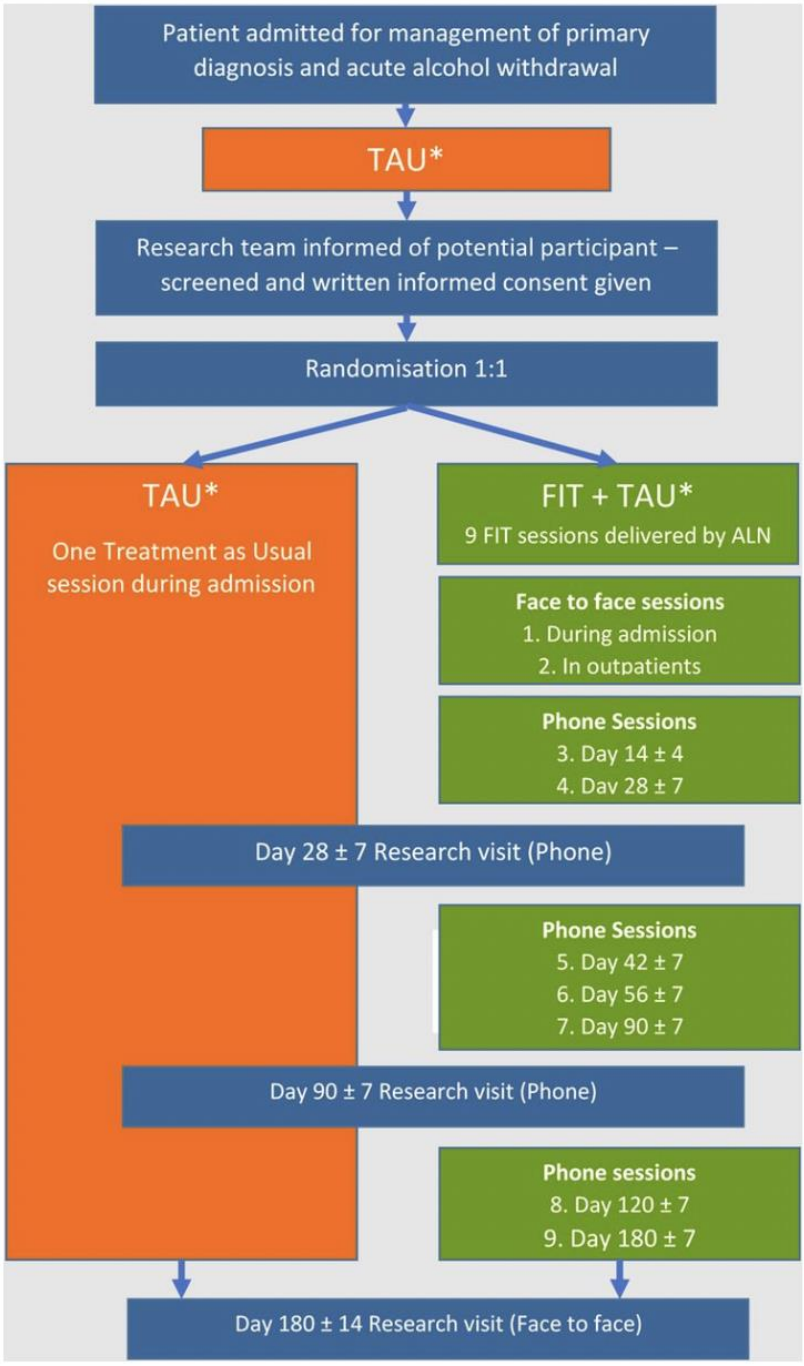
Progression criteria have been agreed by the TSC (table 3). If all the criteria meet the green thresholds, a definitive trial will be planned; if some/all the criteria are in the amber zone, the trial

design will require amendment; if some/all the criteria are in the red zone, all options will be considered including not proceeding to plan a definitive trial.

Table 3. Progression criteria to a definitive trial

Criteria	**Red**	**Amber**	**Green**
Percentage recruited from patients approached	<40	40 – 60	> 60
Percentage of intervention participants completing FIT session 1 **and** either session 2 or 3	< 50	50 – 70	> 70
Percentage of all participants followed-up at proposed primary endpoint of 180 days	< 60	60 – 80	> 80
Percentage of all participants providing valid data for the proposed primary outcome of self-reported alcohol use at proposed primary endpoint of 180 days	< 55	55 – 75	> 75

Figure 1
Trial flow chart showing main trial procedures and visits. *TAU is delivered only once but can take place at any time during hospital admission and may occur before randomisation. ALN, alcohol liaison nurse; FIT, functional imagery training; TAU, treatment as usual.



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