FULL/LONG TITLE OF THE TRIAL

Pilot randomised trial of functional imagery training plus treatment as usual versus treatment as usual alone to reduce alcohol-related harm in patients with alcohol-related liver disease admitted to hospital

SHORT TRIAL TITLE / ACRONYM

Mental imagery to reduce alcohol-related harm in patients with alcohol-related liver damage (MIRAGE)

IRAS number:	**293042**
ISRCTN:	
FUNDER'S number:	**140**

This protocol has regard for the HRA guidance and order of content

Version 1_28.01.2021

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and in accordance with the UK Policy Framework for Health and Social Care Research, the Data Protection Act 2018), the principles of Good Clinical Practice (GCP) and the Sponsor's (and any other relevant) SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: pp  (Assistant Clinical Trials Manager) Date: 09/Mar/2021

Name (please print): Dr Chris Rollinson

Position: Research Governance Manager

Chief Investigator:

Signature:  Date: 09/Mar/2021

Name: (please print): Dr Ashwin Dhanda

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Senior Trial Statistician:

Signature:  Date: 09/Mar/2021

Name: (please print): Professor Siobhan Creanor

Trial Statistician:

Signature:  Date: 09/Mar/2021

Name: (please print): Dr Kara Stevens

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KEY TRIAL CONTACTS

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Trial Steering Committee – Independent members	Dr Paul Richardson (Chair) Consultant Hepatologist, Royal Liverpool University Hospitals NHS Foundation Trust Email: Paul.Richardson@liverpoolft.nhs.uk Dr Christopher Partlett (Independent statistician) Assistant Professor of Medical Statistics and Clinical Trials at Nottingham CTU Email: Chris.Partlett@nottingham.ac.uk Dr Alison Battersby (Independent clinician) Consultant Addiction Psychiatrist, Livewell Southwest Email: Alison.battersby@nhs.net Mr Joe Watson, Patient representative, joseph.marc.watson1@gmail.com Mr Michael Hooper, Patient representative, hoopermichael1980@gmail.com

i. LIST OF CONTENTS

ii. LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
ALN	Alcohol Liaison Nurse
ArLD	Alcohol-related Liver Disease
AH	Alcoholic Hepatitis
AR	Adverse Reaction
AUDIT	Alcohol Use Disorder Identification Test
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EC	European Commission
EQ-5D	European Quality of Life – 5 Domains
ELF	Enhanced Liver Fibrosis test
FIT	Functional Imagery Training
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
JLA	James Lind Alliance
MI	Motivational Interviewing
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SADQ	Severity of Alcohol Dependence Questionnaire
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information

SUSAR	Suspected Unexpected Serious Adverse Reaction
TAU	Treatment as Usual
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRC	UK Clinical Research Collaboration
WEMWBS	Warwick-Edinburgh Mental Wellbeing Scale

iii. TRIAL SUMMARY

Full title	Pilot randomised trial of functional imagery training (FIT) plus treatment as usual (TAU) versus TAU alone to reduce alcohol-related harm in patients with alcohol-related liver disease admitted to hospital
Short title	Mental imagery to reduce alcohol-related harm in patients with alcohol-related liver damage
Trial acronym	MIRAGE
Trial design	Multicentre, parallel group, 1:1 randomised controlled pilot trial
Trial participants	Patients with alcohol-related liver disease (ArLD) and alcohol dependence admitted to hospital
Planned sample size	90
Treatment duration	approx. 180 days from discharge
Follow up duration	approx. 180 days from randomisation
Planned trial period	24 months duration: Trial set-up Months 1 to 6 Participant recruitment Months 7 to 14 Outcome data collection Months 7 to 21 Data analysis and reporting Months 22 to 24
Protocol aim	To conduct a randomised pilot trial of FIT and TAU versus TAU alone
Primary protocol objectives	1. To estimate rates of screening, recruitment, randomisation, retention, adherence to FIT/TAU and possible contamination 2. To allow a preliminary assessment of FIT intervention in the ArLD population
Secondary protocol objectives	1. To estimate the resource use and costs associated with delivery of intervention, 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
Intervention	Functional Imagery Training (FIT) in addition to treatment as usual
Control	Treatment as usual alone

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL SUPPORT GIVEN
The Jon Moulton Charity Trust Trafalgar Court, 2nd Floor, East Wing, Admiral Park, St Peter Port, Guernsey, GY1 3EL helen@jmcharitytrust.gg	**£308,655**

v. ROLE OF TRIAL SPONSOR AND FUNDER

The Sponsor for this study, University Hospitals Plymouth NHS Trust, assumes overall responsibility for the initiation and management of the trial.

The Sponsor and funder will not have direct involvement in trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

The trial was designed by the Chief Investigator and co-applicants with support from the NIHR Research Design Service and the Peninsula Clinical Trials Unit.

vi. ROLE OF THE COORDINATING CLINICAL TRIALS UNIT (CTU)

The Sponsor of the study has allocated tasks associated with overall trial management and data management to the Peninsula Clinical Trials Unit (PenCTU). CTU's management of the trial includes the delivery of site initiation training and monitoring. A detailed breakdown of tasks undertaken by CTU on behalf of the CI and trial Sponsor is described in a formal written Sponsor agreement.

vii. ROLES OF TRIAL OVERSIGHT COMMITEES AND GROUPS

The Trial Steering Committee (TSC) has an independent chair, Dr Paul Richardson, Consultant Hepatologist, Liverpool University Hospitals NHS Foundation Trust. It has an independent clinician, an independent statistician and two patient representatives. The TSC will meet at least every 6 months to review the progress of the trial and any serious adverse events and will report to the Sponsor. Detailed role and remit of the TSC is described in a separate TSC Charter. The TSC is an executive oversight body operating on behalf of the Sponsor and will make decisions as to the future continuation (or otherwise) of the trial.

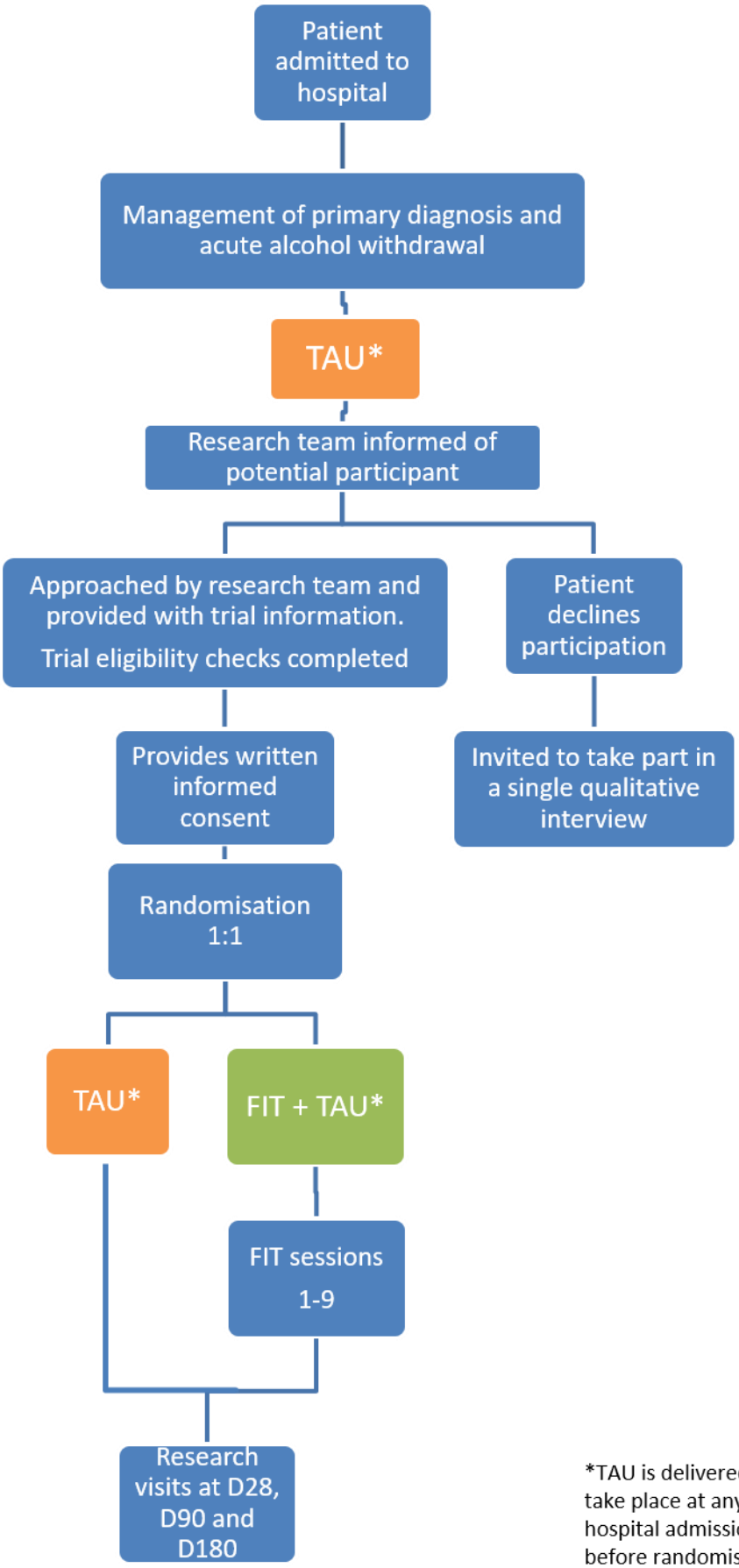
The Trial Management Group (TMG) is chaired by the Chief Investigator and includes a representative from the Sponsor and CTU as well as the trial statistician and two patient representatives. It also has representation from co-investigators and leads for the qualitative and health economic components. The TMG will meet monthly to review trial progress and to ensure appropriate management of the trial.

A Data Monitoring and Ethics Committee will not be convened for this trial which is considered to pose low risk of harm to participants.

viii. KEY WORDS:

Alcohol-related liver disease; alcohol dependence; psychological therapy; mental imagery

ix. PATIENT JOURNEY FLOW CHART



*TAU is delivered only once but can take place at any time during hospital admission and may occur before randomisation.

1. BACKGROUND

Alcohol use results in a high healthcare and economic burden. Alcohol use is the third leading cause of premature death in the UK[1] and is the main driver of chronic liver disease, which is estimated to affect 600,000 people in England alone.[2] 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] Alcohol-related healthcare costs £3.5 billion to the NHS directly and up to £52 billion to the UK economy annually.[3]

ArLD reduces patients' quality of life and survival. It 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[4] (QoL) and survival.[5] Alcohol dependence is characterised by craving, tolerance, a preoccupation with alcohol and continued drinking in spite of harmful consequences.[6] The only effective treatment to prevent progression of liver damage is reducing or ceasing alcohol consumption.[5] Patients who continue to drink heavily develop progressive liver damage[7] and have a higher risk of death.[8] In the most affected group of ArLD patients, those with an acute inflammatory liver injury termed alcoholic hepatitis (AH), two-thirds of patients who survive to hospital discharge relapse to alcohol consumption within six months and have a three- to four-fold risk of death within one year.[9,10] A typical district general hospital in the UK will treat approximately 200 ArLD patients annually but in more deprived, large, urban communities such as in Plymouth, Bristol and Leeds admissions are above average.[2]

Admission to hospital is an opportune time for intervention. Unplanned hospital admission is a crisis point in the ArLD patient's journey. Research on smoking cessation, weight loss, and alcohol reduction shows that medical crises, including disease diagnosis and hospital admission, provide an opportunity for intervention where behaviour change is more likely to result.[11-14]

Treatment as usual (TAU) is a brief intervention, a form of motivational interviewing (MI), conducted by a trained health professional during the in-patient stay, lasting less than 20 minutes and signposting patients to community services, as recommended by NICE.[6] However, early relapse after hospital admission remains a challenge.[9] 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[15]. Trials of multi-session MI report favourable 1-3 year outcomes[16,17] but intervene 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.[18,19]

Pharmacological therapy for alcohol dependence is ineffective in patients with chronic liver disease. 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.[20-22] Uncertainty remains over efficacy, tolerability and dosing of baclofen for patients with liver disease.

We need a brief psychological intervention for ArLD patients that capitalises on receptiveness to change immediately after unplanned hospital admission, as TAU does, and extends support beyond discharge, as multi-session MI does.

Psychological evidence shows that MI can be improved in two ways.[23] Encouraging patients to create vivid multi-sensory images of their goals amplifies desire for them[24,25] and combats cravings.[26] Teaching individuals to use motivational imagery in real-life decision situations – effectively to be their own therapist - supports long-term self-management.[19] Functional Imagery Training (FIT) is a new treatment that does just this, combining the benefits of MI with evidence-based techniques to further strengthen motivation, combat craving, and train self-management skills.[27] In a typical FIT session, participants are encouraged at salient points in a motivational interview 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 participant puts them together into a personal mental 'movie' in which they start working successfully on their plan, playing it through to the end of the week and then to a few months or years in the future when they have achieved their goal. They are encouraged to practice this imagery frequently by pairing it with a routine 'reminder' behaviour like hand-washing. Booster sessions help set new goals and update imagery based on recent successes or drawbacks.

FIT has a strong scientific basis. Substantial research shows that more vivid imagery of seeing, tasting, smelling and swallowing alcohol accompanies stronger alcohol cravings[28,29] and consumption.[30] Imagery of why (incentives) and how (self-efficacy) the person will change also accompanies motivation for functional behaviour change goals, including alcohol reduction.[31,32] An RCT of FIT versus MI for alcohol reduction is ongoing in Australia (ACTRN12616000480482) in a community rather than inpatient sample.

FIT is effective for other behaviours. In a 12-month RCT for weight loss, FIT produced greater mean weight loss than MI (-4.2kg versus -0.7kg at 6 months) and in FIT only, participants continued losing weight after the intervention ended (an additional 2kg lost at 12 months).[19] FIT has also been used in sporting contexts where it increases athletes' resilience.[33] A similar intervention has a benefit in behavioural activation for treatment of depression.[34]

2. RATIONALE

Before running a definitive trial to assess the effectiveness of FIT in patients with ArLD admitted to hospital, we need to find out whether patients with ArLD are interested and willing to take part in randomised trials, how well Alcohol Liaison Nurses (ALNs) can deliver FIT, as well as collecting information to calculate how many patients we would need to recruit in a definitive trial. We will do this in this pilot study by randomising consenting patients to TAU or FIT+TAU and recording rates of recruitment and retention. Alcohol outcome data will provide an opportunity to look for promise of the FIT intervention in the ArLD population as well as allow us to estimate the sample size for a full trial. We will establish and pilot a framework for assessing the cost-effectiveness of FIT in a definitive trial. Qualitative data from ALNs will inform refinement of a FIT training package that can be implemented in the full trial and rolled out across the NHS if the intervention is shown to be effective and cost-effective.

Justification

The evidence (summarised above) demonstrates that existing psychological therapies and pharmacological adjuncts are insufficient in reducing alcohol consumption in patients with ArLD. Novel treatment strategies are required. Patients and clinicians have ranked “What are the most effective ways to help people with alcohol-related liver disease stop drinking?” as the top priority area for research in a recent Priority Setting Partnership undertaken by the National Institute for Health Research and the James Lind Alliance (JLA 2017): It also fits with the NHS long-term plan[35], which has recognised that alcohol-related rea of healthcare requiring investment and improvement and includes a commitment to reduce health inequalities by improving alcohol services.

Patients confirm the need for a new treatment; a survey of Plymouth patients who survived a hospital admission with a complication of ArLD has also identified the need for developing treatment for alcohol dependence. All but one patient surveyed had tried every available avenue of alcohol support, including residential detoxes, group sessions, counselling, motivational interviewing and brief interventions. Despite this, they all continued harmful drinking and developed a complication of ArLD. One patient stated, “I’ve tried everything there is to offer and nothing helps. I would try anything that might work”.

FIT has a strong scientific basis, including research on alcohol use and alcohol reduction.[29,36,37] It has shown a clinical benefit in motivating behaviour change for weight management.[19,37,38] In this study, we will obtain pilot data on whether hospital-initiated FIT delivered in addition to TAU in alcohol-dependent patients with ArLD can be successfully conducted. The trial includes an initial FIT treatment session during the patient’s index hospital admission, followed by a further face-to-face session delivered in an outpatient setting (or virtually if COVID-19 restrictions are in place) within a week of hospital discharge and then regular telephone sessions over the next 6 months.

This pilot trial will not definitively test the effectiveness and cost-effectiveness of FIT treatment in patients with ArLD but will determine whether participants are willing to be recruited to, and remain engaged with, a randomised trial of FIT. A future definitive RCT will answer the question as to whether FIT, in addition to TAU, is superior in terms of clinically meaningful reduction in alcohol consumption, in comparison with TAU only and whether it is cost-effective.

Rationale for treating patients with ArLD in secondary care

We have selected the population of patients with ArLD and alcohol dependence who are admitted to hospital for the following reasons:

- This patient group has most to benefit from alcohol reduction as ongoing alcohol consumption puts them at high risk of developing complications of their liver disease (reduced QoL, increased mortality and morbidity).
- A hospital admission is an opportunity to engage with a group of patients that often do not actively seek support for their alcohol dependency.
- Patients will have received alcohol withdrawal treatment during their hospital stay and they will be free from physical alcohol dependency at the time of planned hospital discharge. The initial hospital stay is an opportune time to intervene with a behavioural intervention.
- The intervention will be delivered by Alcohol Liaison Nurses (ALNs) who are already trained in brief interventions and MI and are already embedded in NHS services. This will facilitate adoption by the NHS, should the planned definitive trial provide evidence that FIT is clinically effective.

3. ASSESSMENT AND MANAGEMENT OF RISK

FIT is a psychological therapy that enhances motivation to change a behaviour. It has been safely used in a variety of situations, including in overweight people and alcohol dependent people in community settings. To our knowledge, there have been no reports of adverse effects of FIT. FIT focuses on helping the individual imagine the benefits of behaviour change compared with the status quo. Imagery is used to strengthen motivation for a future goal, and to develop and build confidence for behavioural plans to achieve that goal. We judge this risk to be low because we shall be intervening at a point where alcohol use has caused sufficient harm to necessitate hospital admission. It is important to note that FIT elicits the person's ideas for future change, focusing on imagining positive benefits of change; it does not delve into the person's psychological history so there is little risk of re-igniting past traumas or exacerbating mental health problems. Any potential harms caused as a result of participating in this research will be detected and addressed in accordance with safety reporting work instructions (see Section 16 Safety Reporting for more details).

4. OBJECTIVES AND OUTCOME MEASURES / ENDPOINTS

Research question for the future definitive trial:

In patients with ArLD and alcohol dependence admitted to hospital, does addition of FIT to treatment as usual, compared to treatment as usual alone, lead to reduced alcohol consumption and alcohol-related harm over 6 months?

To finalise the design of a definitive trial to answer this question, we will firstly undertake this pilot trial with the following objectives.

4.1. Primary objectives

To conduct a randomised pilot trial of FIT and TAU versus TAU alone. This pilot study will provide high quality data:

1. To estimate rates of screening, recruitment, randomisation, retention, adherence to FIT/TAU and possible contamination
2. To allow a preliminary assessment of FIT intervention in the ArLD population.

4.2. Secondary objectives

1. To estimate the resource use and costs associated with delivery of intervention, 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.

4.3. Outcome measures

4.3.1. Pilot trial outcome measures

To facilitate the design and planning of a future definitive trial, we will gather the following outcome measures:

- Recruitment rate (overall and by centre)
- Retention rate at 90 and 180 days (overall and by centre)
- Fidelity of delivery of FIT and TAU (further details below)
- Intervention engagement – number of successful FIT phone calls and visits
- Completeness of data collection.

4.4. Participant reported and other clinical outcomes

The proposed primary outcome for a future definitive outcome is change in 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[39] which is used to determine a patient'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.[40] Self-monitoring, for example keeping a diary of alcohol use, is demanding for the patient, prone to missing data, and has a psychological impact through drawing attention to habitual use. The timeline follow-back method is a systematic tool to record alcohol use and avoids the reactivity of self-monitoring.[41]

Proposed participant reported secondary outcomes for a future definitive trial to be completed at baseline and 28, 90 and 180 days post-baseline are the:

- Severity of Alcohol Dependence Questionnaire (SADQ) is a validated 20 item questionnaire, which correlates with the degree of alcohol dependence[42]
- EQ-5D-5L questionnaire to measure health-related Quality of life
- Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)[43] to measure mental wellbeing (including short form version (SWEMWBS))[44]
- Health, social care and wider care services utilisation will be determined using a resource use questionnaire completed at baseline, day 90 and day 180
- 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).[45]

4.4.1. 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[46].

4.5. Summary of objectives and outcomes

Objectives	Outcome Measures
Pilot Objectives	
Rates of recruitment	Number of patients screened and recruited
Rates of retention	Number of recruited patients attending follow-up visits
Data completeness	Completeness of data capture and outcome measures (to include number of completed questionnaires, number of missing items within a questionnaire by time point)
Fidelity of FIT	Fidelity assessment
Patient reported and other clinical objectives	
Alcohol use	Self-reported alcohol use (grams of alcohol) within preceding 7 days using the timeline follow-back method
Alcohol dependence	SADQ score
Health-related quality of life	EQ-5D-5L
Mental wellbeing	WEMWBS (including SWEMWBS)
Use of health and social care services	Healthcare services utilisation questionnaire
Re-hospitalisation rate	Self-reported
Self-reported time to relapse	Self-reported
Exploratory objectives	
Alcohol consumption	Urine direct alcohol biomarkers (ethyl glucuronide/sulphate)

Table of objectives and outcome measures. Refer to tabulated schedule of events (Section 10) for timings of outcome measures.

5. TRIAL TREATMENTS

All patients will undergo medical management for alcohol dependence and acute alcohol withdrawal with oral benzodiazepines given according to the Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA) and according to local NHS Trust protocols. Patients will receive parenteral vitamin B (pabrinex®) according to local protocol. Patients' clinical problems will be managed by the usual clinical team. These activities will commence before a patient is considered for eligibility for this trial but may continue after recruitment to this trial and baseline data collection.

5.1. Treatment as usual (TAU)

In addition to medical management, patients will be referred to the in-hospital Alcohol Liaison Service and be assessed by an ALN. The ALN will deliver structured Brief Intervention and Advice, tailored to the individual patient and typically lasting approximately 15 minutes. Brief intervention is motivationally-based and can take the form of motivational-enhancement therapy or motivational interviewing: the aim is to motivate people to change their behaviour by exploring with them why they behave the way they do and identifying positive reasons for making change.[47] The brief intervention is based on the FRAMES principles (feedback, responsibility, advice, menu, empathy, self-efficacy) and should cover the potential harm caused by their level of drinking and reasons for changing the behaviour, including the health and wellbeing benefits; cover the barriers to change; outline practical strategies to help reduce alcohol consumption (to address the 'menu' component of FRAMES); lead to a set of goals.[48]

The patient is given information and contact details of their local community alcohol support service and a follow-up appointment is made with them if necessary.

Patients are discharged as determined by their usual clinical team.

TAU may be initiated at any time during a patient's hospital admission. For the purposes of the trial, the initiation of TAU in relation to trial consent, baseline data collection and randomisation will be captured.

5.2. Functional Imagery Training (FIT)

FIT therapy will be provided to participants by trained ALNs according to a separate manual. Session 1 will be delivered in hospital by an ALN and will take approximately 1 hour. It consists of a motivational interview with multisensory mental imagery exercises at intervals where the patient imagines how it would feel to have achieved their goal of alcohol reduction, uses mental imagery to test their ideas for working towards that goal, imagines past successes and applying strategies that worked previously to overcome anticipated obstacles. Session 2 will take place around 1 week after hospital discharge, and focuses on reviewing progress, building confidence and adjusting goals and plans to fit the patient's current circumstances. The patient is encouraged to practice imagery routinely, using everyday tasks like handwashing to remind them and identifying risk points when extended imagery practice would be useful. This session will last up to 45 minutes. Session 3 (30 minutes) will take place via telephone and focuses on incorporating recent successes, however brief, into imagery, adjusting goals or setting new goals, and reinforcing the habit of imagery practice. Sessions 4 to 9 are brief booster phone calls lasting up to 15 minutes and happening at monthly intervals. They focus on identifying successes, setting goals, and updating imagery accordingly.

6. TRIAL DESIGN

Pilot multicentre randomised controlled trial of FIT in addition to TAU versus TAU alone.

6.1. Design considerations for minimising bias

Randomisation: Participants will be randomly allocated, in a 1:1 ratio, to either the intervention group (FIT plus TAU) or the control group (TAU alone), using a web-based randomisation system provided 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 psychological FIT intervention from them.

The outcome assessors (i.e. research team members conducting research visits) will be blinded to treatment allocation. The success of outcome assessor-blinding will be evaluated at each post-randomisation data collection timepoint by asking outcome assessors to record the treatment group to which they think a participant has been allocated in the case report form. This information will be used to assess the success of blinding. Outcome assessors will also be asked to report any cases of inadvertent unblinding (e.g. as a result of the participant disclosing their allocated treatment). Such cases will be documented and reported as protocol non-compliances to the TMG (and will also be reported in the trial write-up). Where possible, the TMG will implement measures to minimise further instances of inadvertent unblinding and will endeavour to ensure that future outcome assessments are performed by a blinded assessor where practicable.

The initial data export provided to the trial statistician undertaking the analyses will not disclose the treatment allocations, so that the analyses of the participant-reported outcomes, as well as the recruitment and retention rates, are completed blinded. In the event that the Trial Steering Committee (TSC) requests unblinded or disaggregated data during the trial, in order to fulfil its data monitoring duties (see section 19.2), members of the PenCTU not involved in the conduct of the trial will assist with preparation of the data and transmission to TSC members, in order to maintain blinding of the trial statisticians.

7. TRIAL SETTING

Multicentre trial conducted in three NHS secondary care trusts: University Hospitals Plymouth NHS Trust, University Hospitals Bristol and Weston NHS Foundation Trust and Leeds Teaching Hospitals NHS Trust.

8. PARTICIPANT ELIGIBILITY CRITERIA

8.1. Inclusion criteria

Patients must satisfy all of the following criteria to be enrolled in the study:

- Adult patients ≥18 years
- Able and willing to provide informed consent
- 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
- High risk alcohol consumption[6] (>50 units/week for males and >35 units/week for females) within 4 weeks prior to hospital admission
- AUDIT score[49] >15 during current hospital admission
- Diagnosis of alcohol dependence as defined in ICD-10[50] 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.

8.2. Exclusion criteria

Patients who meet any of the following criteria will be excluded from study participation:

- Any condition with an estimated life expectancy of less than 6 months
- Patients participating in concurrent interventional research
- Participants 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

9. RECRUITMENT AND CONSENT

Site Principal Investigators will be responsible for promoting the study amongst relevant staff at their hospitals in order to optimise participant recruitment. Recruitment performance at each site will be closely monitored by the Trial Management Group (TMG).

9.1. Participant identification

Potential participants will have been admitted to hospital via the emergency department or medical or surgical receiving units for treatment of their condition, which may or may not be related to ArLD. According to local NHS trust protocols at each participating centre, all patients with alcohol dependence will be referred to an alcohol liaison nurse (ALN) who will review them within 24 hours of receiving the referral. Many patients will also be under the care of a hepatologist. Therefore, the treating clinical team will be able to identify potential trial participants. Members of the research team will not require access to identifiable patient data for the purpose of identifying potential participants.

9.2. Eligibility screening

Potential participants will be initially approached about the study by a member of the usual clinical care team. With the patient's agreement, they will be referred to the research team who will provide detailed written information about the study and to screen the potential participant for eligibility. A clinician or senior nurse from the research team will assess eligibility by reviewing the patient and their medical record against the defined eligibility criteria (section 8). No additional screening assessments are required. A log of all patients screened will be recorded (see section 9.4).

There is currently no provision available to conduct FIT treatment in languages other than English and all participant-facing trial documentation is written in English. As such, patients who are deemed to have significant difficulties in adequate understanding of English shall be deemed ineligible. Sufficient understanding of English should be evaluated during the informed consent process (see section 9.3).

Patients who may be suitable for the trial but lack capacity to provide informed consent are also deemed ineligible (assessment of capacity described in Appendix 1). However, such patients may be re-considered as a potential trial participant should they regain mental capacity. As part of standard care, the treating clinical team will assess capacity each day and can refer a potential trial candidate back to the research team for re-screening. Patients who fail screening due to inability to provide

informed consent can be screened on one further occasion after an interval of at least 24 hours. An assessment of capacity should be performed during the informed consent process (see section 9.3).

Patients who are deemed eligible will be invited to provide informed consent.

9.3. Consent

The site Principal Investigator (PI) or an authorised delegate must obtain informed consent prior to the collection of any baseline data. Authorised delegates must be suitably trained in the relevant principles of Good Clinical Practice and the requirements of the trial protocol. Training materials will be provided by the coordinating clinical trials unit (Peninsula Clinical Trials Unit (PenCTU)). Doctors and registered nurses (band 5 or higher) may be authorised to obtain consent in this study.

The process of obtaining informed consent must include:

- discussion with the potential participant about the nature and objectives of the study and possible risks associated with their participation
- the provision of the approved Participant Information Sheet (PIS) and consent document
- the opportunity for potential participants to ask questions
- an assessment of capacity to consent (see Appendix 1)
- advising the potential participant that they have the right to refuse participation without giving reasons and that they are free to withdraw at any time without giving reasons and without prejudicing his/her further treatment
- advising the potential participant on how their data will be used and signposting to further information about data used for research purposes
- advising the potential participant about the payment available for completion of the study (see section 9.3.1)

The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

Potential participants shall be given sufficient time (at least 24 hours) to consider the written information provided and to discuss the study with a member of the research team who will be knowledgeable about the research. Whilst at least 24 hours will be provided, participants may provide consent sooner if they wish.

The member of the research team and the participant will complete the approved Informed Consent Form (ICF). If a participant is not able to read the text and/or sign for themselves but has capacity to give consent, a witness will confirm that the participant has accurately read the consent form and had the opportunity to ask any questions and received satisfactory replies. A witness will be permitted to sign on a participant's behalf if the participant has difficulty with reading or writing English, provided that the extent of difficulty is not grounds for exclusion.

Where a participant can consent for the trial but later becomes incapacitated, the participant will be withdrawn from the trial because FIT therapy will not be possible. No further treatment or research visits will be completed. See section 13.

Original versions of completed ICFs should be stored in the Investigator Site File (ISF). One copy should be provided to the participant for him/her to retain, a copy should be filed in the hospital notes/electronic health record and a de-identified copy should be provided to the CTU for central monitoring purposes (see section 19).

9.3.1. Payment

To acknowledge the additional burden of trial procedures and 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. Participants will be reimbursed reasonable travel expenses for attendance at hospital for the research visit at 6 months.

9.4. Recording screening and recruitment information

Given the pilot nature of this trial, investigator sites will be required to keep accurate records in the provided Screening Log of:

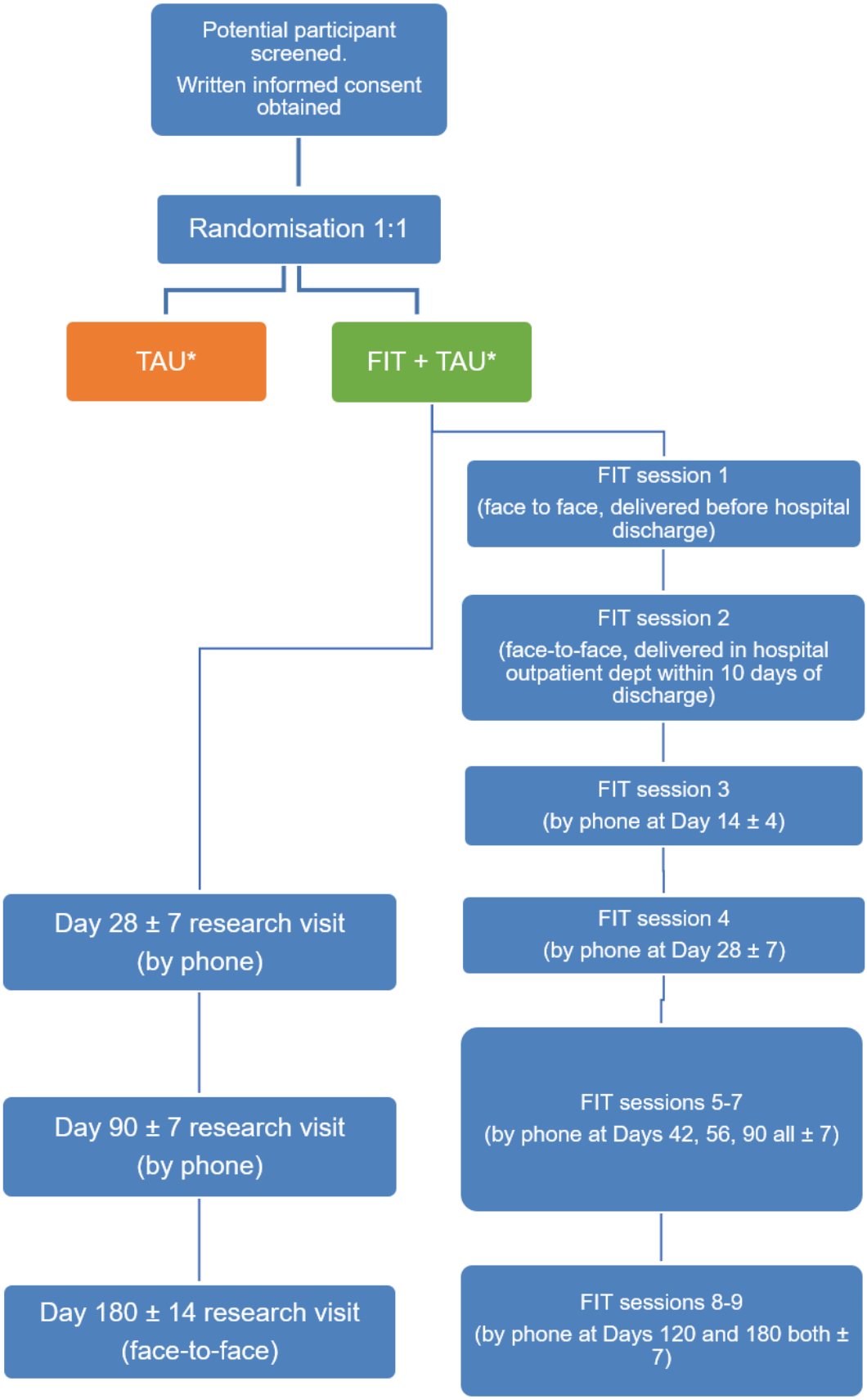
- the number and characteristics* of potential participants referred to the research team
- the number and characteristics* of patients screened for eligibility by the research team
- the number and characteristics* of patients deemed ineligible (with reasons where available)
- the number and characteristics* of patients provided with a PIS
- the number and characteristics* of patients declining to give consent (with reasons where available)

*characteristics in this case means age, gender and ethnicity (if applicable). Information collected in order to report generalisability of the study population.

10. TRIAL SCHEDULE

This section describes the conduct of the trial in chronological order, detailing procedures for data collection at each of the time points. A summary flow chart is provided in Figure 1. A tabulated

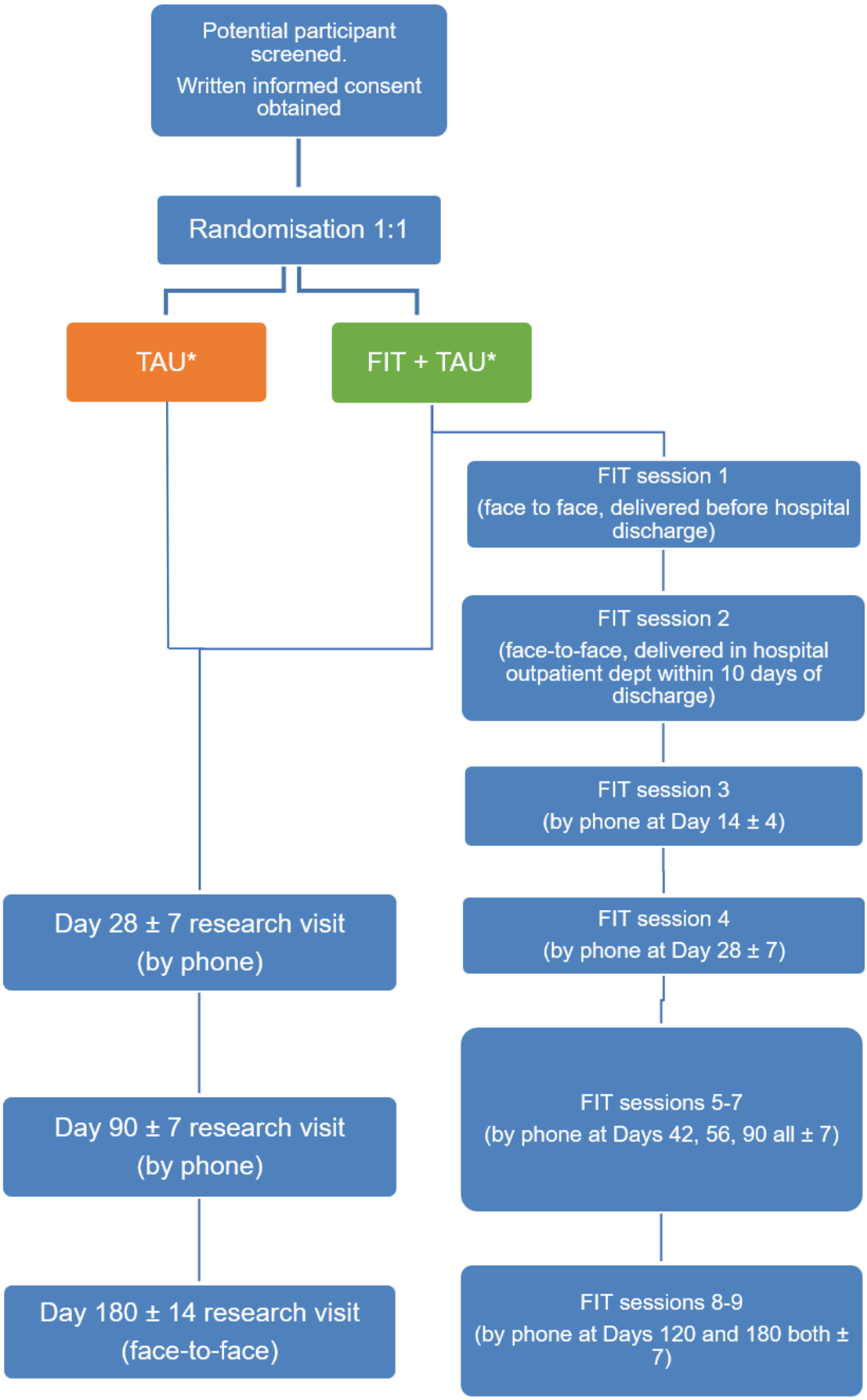
summary of the trial schedule is given in



*TAU is delivered only once but can take place at any time during hospital admission and may occur before randomisation.

Table 1. The trial involves four research visits (two face-to-face and two by telephone), each lasting approximately 60 minutes.

Figure 1: Trial Flowchart



*TAU is delivered only once but can take place at any time during hospital admission and may occur before randomisation.

Table 1: Tabulated summary of trial

	Pre-baseline	Baseline	Allocation	Post-allocation		
TIMEPOINT		t_0		*+28 days* t_1	*+90 days* t_2	*+180 days* t_3
ENROLMENT:						
Eligibility screen	X	X				
Informed consent		X				
Demographics		X				
Medical History (Liver disease, Co-morbidities)		X				
Historical Alcohol and Substance Use		X				
Concomitant medications		X				
/Allocation			X			
INTERVENTIONS:						
Intervention Group: ***FIT***		◆———	———	———	———	———◆
Intervention Group: ***TAU***	◆———	———	———◆			
Control Group: ***TAU***	◆———	———	———◆			
ASSESSMENTS:						
SADQ Score		X		X	X	X
Current alcohol use†		X		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
SAFETY MONITORING:						
Adverse event reporting		◆———	———	———	———	———◆

†Self-reported alcohol use (units of alcohol) over a period of 7 days obtained using the timeline follow-back method (see section 10.1.1). 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)

10.1. Baseline

After written informed consent has been obtained, the PI (or authorised delegate) will collect the following information from participants:

Demographics

- Age
- Gender
- Ethnicity
- Age at completing formal education
- Employment status
- Occupation (current or most recent)
- Housing status
- Co-habitants
- Marital/partner status

Liver disease

- Date of diagnosis of liver disease (as documented in medical record)
- Stage of liver disease (fatty liver only/fibrosis/cirrhosis)
- If cirrhosis, Model of End-stage Liver Disease (MELD) and Child Pugh scores
- Known co-factors (e.g. viral hepatitis, metabolic disease, haemochromatosis)

Alcohol use

- Number of units of alcohol consumed in the week immediately prior to hospital admission (using timeline follow-back method; see section10.1.1)
- AUDIT score
- SADQ score
- Self-reported duration of problematic alcohol use
- History of alcohol withdrawal seizures

Substance use

- History of drug or substance misuse (type of substance, frequency and duration of use)

Co-morbidities

- Medical and surgical diagnoses
- Mental health diagnoses

Concomitant medications

- List of regular prescribed and over-the-counter medications taken within 7 days prior to hospital admission

Health-related quality of life

- EQ-5D-5L questionnaire

Mental wellbeing

- WEMWBS questionnaire (including SWEMWBS)

Health, social and wider care services utilisation

- Health, social and wider care services utilisation questionnaire including primary, secondary and social care interactions
- Number of hospital admissions in previous 6 months (from medical records)
- Number of alcohol-related hospital admissions in previous 6 months (from medical records)
- Number of Emergency Department attendances in previous 6 months (from medical records)

Delivery of TAU

- Brief intervention and advice session: date and time of delivery, duration of session and role designation of person who delivered the session.

Data collected will be captured on worksheets and entered by members of the research team into the electronic Case Report Form (eCRF). Worksheets and eCRF system will be provided by PenCTU (see section 18).

10.1.1. Collection of alcohol consumption using timeline follow-back method

The timeline follow-back method is a systematic tool to record alcohol consumption over a given period. The research team will be trained in applying this method and provided with a worksheet to structure and record the assessment.

10.1.2. Collection of participant contact details

Participants will be asked to provide a primary contact telephone number in order to facilitate arrangement of treatment and research visits. They will also be asked to provide a secondary contact number of a suitable friend or relative who is in regular contact with them.

10.1.3. Randomisation

After all baseline data collection is complete, the participant will be randomly allocated to either the intervention group (TAU+FIT) or the control group (TAU alone). Treatment allocation will be achieved by a web-based system created by PenCTU in conjunction with a statistician independent of the trial team. Participants will be 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).[42]

A member of the research team will access the online randomisation system and enter the information requested. The randomisation system will return confirmation that the participant has been successfully randomised.

Confirmation that randomisation has been performed will be communicated in a blinded fashion to investigator site staff and key members of the central research team. Communication will be achieved via emails automatically generated by the randomisation system.

Further automatically generated emails will be sent to the PI and ALN(s) at the relevant site, advising that a participant has been randomised and disclosing the treatment group to which the participant has been allocated.

ALN(s) will be responsible for informing participants of their allocation and initiating the allocated treatment. ALNs must record initiation of treatment in the eCRF as soon as possible, noting that TAU may be delivered at any point during a patient's hospital admission, and so may have already been administered at the point of randomisation.

Participants allocated to the control group will receive TAU as described in section 5.1.

Participants allocated to the intervention group will commence FIT treatment as described in section 10.5 in addition to the TAU provided by the local clinical team.

PenCTU staff independent of the trial will verify the integrity of the randomisation system throughout the trial according to established written procedures.

10.1.4. Before hospital discharge procedures

Before the participant is discharged, the research team member will ensure that the participant is advised when the next contact will be made and that the contact details provided are correct. At, or soon after, the end of the baseline visit, the research team member(s) will ensure that:

- the participant's GP is informed (using the approved GP letter)
- participation in the study is recorded in the patient's hospital record by documenting a record of the baseline visit and record of TAU (if this was completed after baseline visit), filing a copy of the completed consent form and GP letter, and flagging that those records belong to a research participant in accordance with local site policy
- Data are entered into the eCRF according to instructions provided by CTU

10.2. Day 28 (± 7 days) visit (by telephone)

A member of the research team will contact the participant by telephone as described in section 10.6. Participants will be asked to avoid disclosing their treatment allocation during the call. The following data will be captured by the research team member on worksheets and entered into the eCRF:

- Number of units of alcohol consumed in the preceding week (using timeline follow-back method; see section 10.1.1)
- SADQ score
- Health-related quality of life
    - EQ-5D-5L
- Mental wellbeing
    - WEMWBS (including SWEMWBS)
- Adverse events (see section 16)

A record of the call will be made in the patient health record.

10.3. Day 90 (± 7 days) visit (by telephone)

A member of the research team will contact the participant by telephone as described in section 10.6. Participants will be asked to avoid disclosing their treatment allocation during the call. The following data will be captured by the research team member on worksheets and entered into the eCRF:

- Number of units of alcohol consumed in the preceding week (using timeline follow-back method; see section 10.1.1)
- SADQ score
- Health-related quality of life
    - EQ-5D-5L
- Mental wellbeing
    - WEMWBS (including SWEMWBS)
- Health, social and wider care services utilisation questionnaire to cover period since hospital discharge
- Adverse events (see section 16)

A record of the call will be made in the patient health record.

10.4. Day 180 (± 14 days) end of trial visit (face-to-face)

A member of the research team will contact the participant by telephone in advance of the end of trial visit to make the necessary arrangements, as described in section 10.6. Participants will be asked to

avoid disclosing their treatment allocation during the visit. During the visit, the following data will be captured by the research team member on worksheets and entered into the eCRF:

- Number of units of alcohol consumed in the preceding week (using timeline follow-back method; see section 10.1.1)
- SADQ score
- Health-related quality of life
    - EQ-5D-5L
- Mental wellbeing
    - WEMWBS (including SWEMWBS)
- Health, social and wider care services utilisation questionnaire to cover period since Day 90 research visit
- Adverse events (see section 16)
- Biochemistry (sample collection and handling described in section 15)
    - Urinary direct alcohol biomarkers (ethyl sulphate and ethyl glucuronide)

There is an option to conduct this session by telephone or virtually in the situation where local or national lockdown measures are implemented to control COVID-19 or after an appropriate risk assessment is made by the local NHS Trust R&D department necessitating reduced footfall within the hospital. In this event, specimen containers and instructions for collection of the urine specimen will be sent directly to participants. They will be asked to return the samples to the appropriate laboratory by prepaid postal delivery.

10.5. FIT treatment sessions

A detailed description of the full protocol for the FIT treatment sessions is provided in a separate manual. After each session, the ALN will record on an eCRF whether the session was completed, the date, time and duration of the session and whether the session was audio recorded for fidelity assessments (see section 10.5.5). In brief the following sessions take place.

10.5.1. Session 1 (in-patient)

This in-patient 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. The ALN uses active listening skills to elicit the participant's personal incentives for change, to explore the discrepancy between how they are now and how they want to be in the future, and to elicit ideas about how to change. Mental imagery is used at each point to strengthen desire for change; to mentally rehearse plans and strengthen commitment to them; to explore ways to overcome barriers; to strengthen confidence by replaying past successes and strategies.

10.5.2. Session 2 (face–to-face)

This second face-to-face session takes place within 10 days of discharge from hospital

The session lasts less than 45 minutes and is included to support motivation early after hospital discharge. This session will take place in the hospital outpatient department to review progress. Imagery is used to help solve any problems with progress towards their goal and to motivate new sub-goals. Individuals who experience strong cravings are taught how to switch their attention deliberately away from their craving imagery and onto their goal imagery.

There is an option to conduct this session by telephone or virtually, in the situation where local or national lockdown measures are implemented to control COVID-19 or after an appropriate risk assessment in made by the local R&D department necessitating reduced footfall within hospitals.

10.5.3. Session 3 (by telephone)

This session takes place at Day 14 (±4 days) post-hospital discharge

The ALN will contact the participant by telephone as described in section 10.6. This session lasts less than 30 minutes. Booster calls affirm progress, develop imagery about recent successes, problem solutions, new goals or behaviours, and encourage practice.

10.5.4. Sessions 4-9 (by telephone)

These six sessions take place at Days 28, 42, 56, 90, 120 and 180 (all ±7 days) post-hospital discharge.

The ALN will contact the participant by telephone as described in section 10.6. All sessions last less than 15 minutes.

10.5.5. Intervention fidelity assessment

Where participants consent, FIT and TAU sessions will be audio recorded for fidelity checking and assessment of contamination. Sampling for fidelity assessment will take place as follows:

- Two FIT sessions will be assessed per ALN (one each from Sessions 1 and 2) from the first five participants and two FIT sessions per ALN (one each from Sessions 1 and 2) from the next five participants.
- Two TAU sessions will be assessed per ALN from each of the first and second sets of five participants.

A trained FIT practitioner will check each ALN's fidelity early in the trial using dedicated fidelity assessment tools previously developed. Feedback and supervision will be provided through these sessions. These fidelity assessments will also examine the potential for contamination due to the same ALNs providing both TAU and FIT.

10.6. Contacting participants for research and treatment visits

A member of the site team (ALN or research team member) will contact the participant by phone at an agreed time. If the participant does not answer, and they have a voicemail service, a short message will be left asking the participant to call back. If they do not call back, or there is not a voicemail service, a second attempt will be made on the same day to the primary contact number of the participant. Failure to be contacted on the second attempt will result in a third attempt on the primary contact number within the following 3 days. If it is still not possible to contact the participant on the third attempt, the secondary contact number will be called and a different contact time organised with the participant via the secondary contact if possible. Where the participant can still not be contacted, no further attempts will be made until their next scheduled visit.

The participant's GP may be contacted by a member of the site team at this point to check patient status.

11. QUALITATIVE ASSESSMENTS

11.1. Participant interviews

Short telephone interviews will be conducted in the first three months of recruitment, with those who were eligible but declined to take part (n=6, 2 from each recruiting site) to identify their reasons for this. At the time they declined to participate in the trial, eligible patients will be asked if their contact details can be retained so that they can be contacted by a named researcher to take part in a voluntary telephone interview.

At the end of the trial, after follow-up visits have been completed, participants who agreed to be further contacted to take part in an interview (control, n=6; intervention, n=9) will be interviewed by telephone to inform our understanding of acceptability and feasibility of trial methods. There will be a focus on study materials, motivation for taking part, understanding and experience of randomisation and, additionally, for intervention participants, engagement with FIT.

At least 24 hours before the interview takes place, the selected interviewees (i.e. patients who declined to take part and participants who completed the study) will be given a separate information sheet describing what is involved in the interview and what will happen to their data. Informed consent will be obtained either in writing by returning the signed informed consent form by post to the researcher at the University of Plymouth or by audio recording of verbal consent. Participants who consent to a telephone interview at the end of the trial 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 >4 FIT sessions versus those that did not).

11.2. Research nurses

Research nurses involved in collecting trial data will be invited to virtual meetings monthly during the first three months of recruitment (which will include the first two months of follow up assessments) to assess recruitment and retention rates and use 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.

11.3. 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. They will be provided with a written information sheet detailing the purpose of the focus groups and what will happen to their data at least 24 hours before the first focus group. Informed consent will be obtained either in writing by returning the signed informed consent form by post to the researcher at the University of Plymouth 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

11.4. 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 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.

12. ECONOMIC EVALUATION

This pilot study will be used to 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 full 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 future CEA will synthesise cost and outcome data to present an incremental cost-effectiveness ratio (ICER) for the primary economic endpoint of policy relevance (cost per quality-adjusted life-year [QALY]). The economic evaluation will follow the internationally recognised Consolidated Health Economic Evaluation Reporting Standards (CHEERs) guidelines for reporting cost-effectiveness studies.[51] A Health Economics Analysis Plan (HEAP) will be developed and agreed prior to database lock.

12.1. Intervention costing

The resources required to deliver the FIT intervention will be assessed via participant-level case-records, and discussion with the intervention developers and providers. This will include ALNs' time, travel, materials, documentation and consumables. ALNs' time will be documented in terms of per-participant contact and non-contact time, and any additional time in relation to delivery of the intervention. Training and supervision resources will also be documented.

Nationally recognised UK unit costs for health and social care services[52] will be applied to this resource use data. Where national costs are not available, costs will be identified in consultation with the intervention developers and providers. The mean cost per participant of the intervention will be estimated.

12.2. Health, social and wider care resource use

A self-report bespoke resource use questionnaire will be developed with our PPI group. This questionnaire will also be informed by the Database of Instruments for Resource Use Measurement (DIRUM)[53] and the core items for a standardised resource use measure.[54]The questionnaire will be completed by participants at baseline and Day 90 and Day 180 follow-ups.

12.3. Quality-adjusted life-years

Participants will complete the EQ-5D-5L[55] at baseline and at Day 90 and Day 180 follow-ups. The EQ-5D is a generic measure of health-related quality of life. It is the instrument recommended for use by the National Institute of Health and Care Excellence (NICE) in health technology assessments to estimate the cost-per-QALY of interventions and to inform healthcare policy across the NHS. In accordance with the current 'position statement' of NICE,[56] 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.[57,58]

13. PARTICIPANT WITHDRAWAL

13.1. Withdrawal from treatment

Given the low risk of harm posed by FIT therapy, withdrawal of the FIT intervention on the grounds of safety or wellbeing concerns is not foreseen. However, if the PI (or authorised delegate) identifies deterioration in psychological state or other relevant medical concerns, s/he may choose to discontinue the FIT treatment.

Participants may choose to withdraw themselves from FIT or TAU intervention at any stage of the trial. In this case, participants will be asked to provide a reason for withdrawal but must be made aware that they are not obliged to give a reason and that their decision to withdraw will not affect their ongoing treatment.

Withdrawal from FIT or TAU and the reason, if known, should be clearly documented in the participant's clinical records and reported to the CTU according to instructions provided.

Withdrawal from treatment does not preclude the participant from remaining in follow-up. All participants withdrawn from FIT or TAU will be encouraged to continue with study visits and assessments as per protocol.

13.2. Withdrawal from follow up

All participants will be encouraged to complete study follow-up, but participants may choose to withdraw from follow-up at any time. In this case, participants will be asked to provide a reason for withdrawal but must be made aware that they are not obliged to give a reason and that their decision to withdraw will not affect their ongoing treatment.

Withdrawal from trial follow-up and the reason, if known, should be clearly documented in the participant's clinical records and reported to the CTU according to instructions provided. Data collected prior to withdrawal from follow-up will be included in the study analysis. Participants will be provided with a contact point where he/she may obtain further information about the study.

Withdrawn participants will not be replaced with new participants.

14. END OF TRIAL DEFINITION

Participants will complete their involvement in the trial after approximately six months, at either the end of trial visit, approximately 180 days after the baseline visit, or at the end of the final FIT delivery session (if in the intervention group), approximately 180 days after hospital discharge. A sample of participants will be selected to take part in qualitative interviews (see section 11). The trial will end on completion of all data collection, including qualitative interview data.

15. COLLECTION, STORAGE AND ANALYSIS OF CLINICAL SAMPLES

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the 2018 Data Protection Act. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

The following clinical samples will be obtained:

- A urine sample for direct alcohol metabolites - at Day 180

Detailed instructions on the collection, recording and processing of samples will be provided to sites in a separate manual, provided by PenCTU.

15.1. Urine

A sample of 10 mL mid-stream urine will be collected into a sterile universal container. It will be stored locally at each site at between -20°C and -80°C in a temperature monitored freezer. After the final trial visit is completed at each site, urine will be sent in a single batch to the Viapath laboratory at King's College Hospital, London for analysis of ethyl glucuronide and ethyl sulphate by liquid chromatography tandem mass spectrometry.

15.2. Destruction of samples

Any samples remaining after the planned analyses will be destroyed in accordance with laboratory standard operating procedures.

16. SAFETY MONITORING

Whilst participants are unlikely to experience any harm as a direct result of taking part in this trial, processes will be implemented to ensure that such harms are detected and monitored appropriately. The safety of participants will be monitored throughout the trial, from the time that consent is obtained until the end of trial visit.

16.1. Definitions

An **Adverse Event (AE)** is any unfavourable sign, symptom, or disease in a participant, regardless of severity and regardless of cause.

An **Adverse Reaction (AR)** is an adverse event which is considered to have been definitely, probably or possibly caused by either the FIT intervention or the trial procedures.

A **Serious** Adverse Event (SAE) or **Serious** Adverse Reaction (SAR):

- results in death
- is life-threatening*
- requires inpatient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability/incapacity
- is a significant or important medical event

*The term "life-threatening" in this context 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.

Hospital admissions for elective procedures **will not be reported as SAEs. All unplanned hospital admissions will be reported as SAEs, regardless of duration of hospital stay. This includes visits to ED departments.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is an event which:

- is serious, as defined above, **and**
- is considered to have been definitely, probably or possibly caused by either the FIT intervention or the trial procedures, **and**
- is deemed ‘unexpected’ i.e. the reaction is one which has not been foreseen by the Chief Investigator.

Guidance on assessing events against these definitions is described later in this section.

16.2. Adverse event reporting in the MIRAGE trial

The likelihood of participants being harmed by either the FIT intervention or any of the trial procedures is very low. As such, the collection and reporting of adverse events in the MIRAGE trial is restricted to only those events which are serious, as defined above. In the context of clinical care and in accordance with local practice, adverse events should be recorded by investigator site staff in the participants’ medical records. For the purposes of the trial, only serious adverse events (including serious adverse reactions) will be collected and entered into the eCRF.

16.3. Detecting and recording serious adverse events

Detailed instructions for the recording and reporting of serious adverse events will be provided to Investigator Sites by PenCTU.

The primary means of detecting serious adverse events will be the interactions between the research team member(s) and the trial participant at each of the data collection timepoints. At each visit or telephone call, participants will be asked to describe any adverse events they have experienced.

Any events meeting the criteria for seriousness (defined in section 16.1) must be recorded by the research team member in the participant's health record and in the eCRF. SAEs are subject to expedited reporting so must be processed in a timely manner (see section16.5).

The Day 90 and Day 180 timepoints involve collection of health and social care resource utilisation. Site researchers should ensure any (non-elective) hospitalisations or ED visits reported by participants when recalling resource utilisation are reported as serious adverse events.

16.3.1. Serious adverse events detected by ALNs during FIT sessions

ALNs may also become aware of hospitalisations experienced by participants if discussed during FIT intervention sessions. In the event that an ALN believes a participant has suffered a serious adverse event caused by the FIT intervention or by any trial procedures, s/he must report immediately to the site Principal Investigator, who will enter the event into the eCRF according to instructions provided by CTU.

16.4. Assessing causality of serious adverse events

For serious adverse events, the PI (or authorised delegate) will assess the causal relationship between the SAE and trial participation.

For participants in the intervention group, the PI will record their opinion on whether or not the SAE was caused by the FIT intervention, and whether or not the SAE was caused by any trial procedures. For participants in the control group, the PI will record their opinion on whether or not the SAE was caused by any trial procedures.

Causal relationship will be recorded in the participant's health record and in the eCRF. SAEs caused by the intervention or trial procedures in the opinion of the PI will be regarded as serious adverse reactions (SARs).

16.5. Reporting Serious Adverse Events and Serious Adverse Reactions

All SAEs and SARs must be reported to PenCTU within 24 hours of the research staff becoming aware of the event, according to instructions provided by PenCTU.

For each SAE/SAR the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causal relationship

PenCTU will immediately notify the CI of any reported SAEs / SARs and the CI will record a second assessment of causal relationship. The CI may upgrade the causality assessment (e.g. from not related to related) but may not downgrade the assessment (e.g. related to not related).

Where a causal relationship is suggested, the CI will record an assessment of expectedness. Expectedness will be judged on a case-by-case basis.

An event deemed to be unexpected will be regarded as a SUSAR and will be subject to expedited onward reporting as described in sections 16.6 and 16.7.

Events will be followed up until the event has resolved or a final outcome has been reached.

16.6. Onward reporting of SAEs / SARs / SUSARs

Onward safety reporting activities and responsibilities are summarised in **Table 2**.

Table 2: Onward safety reporting activities and responsibilities

Event	Reported by	Reported to	Reported when	Reported how
SUSARs	PenCTU	Sponsor	Within* 24 hours	Email to crollinson@nhs.net and cc h.allende@nhs.net
SUSARs	PenCTU	REC† & TSC‡	Within* 7 or 15 days¶	Using non-CTIMP safety report form (available on HRA website), by email.
All SAEs/SARs	PenCTU	Sponsor & TSC	Quarterly	Line listing, by email
Overall safety concerns	PenCTU	REC	Annually	Using annual progress report form (available on HRA website), by email

**of the CI becoming aware of the event*
†*REC - Research Ethics Committee*
‡*TSC - Trial Steering Committee*
¶*7 days for fatal or life-threatening events. 15 days for others*

16.7. Unblinding for SUSAR reporting purposes

SUSARs will be unblinded before onward reporting to the REC. Unblinding will be performed by designated member(s) of PenCTU.

16.8. Coding of adverse events

PenCTU will maintain a register of all recorded serious adverse events. Events entered into the eCRF will be coded by designated members of PenCTU staff using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 23.1. Events will be coded at two levels - the 'preferred term' (PT) and 'System organ class' (SOC). The same version of the MedDRA dictionary will be used throughout the trial.

16.9. Safety oversight

The Trial Management Group (TMG) will discuss any SUSARs and any emerging safety concerns at monthly TMG meetings. Line listings of SAEs/SARs, produced by PenCTU, will be reviewed quarterly by the Trial Steering Committee (TSC) in accordance with the details set out in the agreed TSC Charter.

17. STATISTICS AND DATA ANALYSIS

17.1. Target sample size and justification

One of the key objectives of this pilot study, to inform the definitive trial, is whether patients can be successfully recruited and followed-up. We estimate that across all three sites, 24 potentially eligible ArLD patients are admitted per month. Allowing for staggered site set-up and a 7-month recruitment window, we anticipate screening ~150 patients; with a conservative recruitment rate of those screened of 60%, our recruitment target is 90 participants (~30/site).

This recruitment target will allow estimation of the overall retention rate with a 95% confidence interval (CI) of at least ±11%. Assuming a non-differential retention rate of 75% at 6-month follow-up, indicates primary outcome data will be available from a minimum of 33 participants within each allocated group, allowing appropriate estimation of key components, such as the variability in the primary outcome, to inform the sample size calculations for the definitive trial.

17.2. Statistical analysis plan

A statistical analysis plan (SAP)[59] will be drafted by the trial statisticians, following CONSORT guidance for pilot and feasibility studies and taking note of the CONSORT extension for reporting of patient-reported outcomes[60,61] The SAP will be reviewed by the TSC and signed off by an independent statistician prior to database lock.

As this is a pilot study, there will be no formal hypothesis testing, instead the focus will be on presenting summary statistics with appropriate confidence intervals,[62] to meet listed primary study objective 2 (see section 4.1). The primary descriptive analyses will be on an intention to treat (ITT) basis.

17.3. Summary of baseline data and flow of patients

The analysis and reporting of this pilot study will follow the CONSORT guidance for pilot and feasibility studies.[60] The flow of participants through the study will be presented in a CONSORT-style diagram with reasons for discontinuation or withdrawal given where available. Descriptive statistics of participants' demographic and baseline characteristics will be presented by allocated groups and overall. No formal between-group comparisons of baseline data will be undertaken.

17.4. Outline of statistical analyses

Trial science outcomes, such as recruitment and retention rates, completeness of outcome measures at each follow-up, will be presented as frequencies and percentages (with confidence intervals), overall and by allocated group where relevant. The timing and frequency of missing outcome data will be summarised. Individuals lost to follow-up will be compared to those who complete the pilot study to identify any potential bias.

Descriptive statistics of the participant-reported and clinical outcomes will be produced, as appropriate for each measure for each group at all timepoints. Changes, where appropriate, between baseline and 6-months will be summarised descriptively and presented by allocated group. Interval estimates of the potential intervention effect of FIT+TAU, relative to TAU only, will be produced, with the promise of the FIT intervention (as per section 4.1, objective 2) assessed using the confidence interval for the between-group difference in change in grams of pure alcohol consumed in previous week (proposed primary outcome for definitive trial).

17.5. Participant population

As described above, the primary descriptive comparative analyses of the participant-reported and other clinical outcomes will be on an intention-to-treat basis, including all the outcome data obtained from all participants, with participants analysed in the group to which they were originally allocated. Safety data (SAEs and SARs) will be presented on a per-protocol basis.

17.6. Procedure(s) to account for missing or spurious data

Reasons for being unable to collect data during an assessment will be recorded on the case report form where appropriate. Case report forms will be assessed for missing data by the CTU. As this is a pilot study, no imputation of missing data will be undertaken with the exception of instances where there are published methods for managing missing items in validated patient-reported outcomes.

18. DATA MANAGEMENT

Data management activities are summarised in this section. Detailed data management activities are described in a separate Data Management Plan (DMP).

18.1. Data collection tools and source document identification

A web-based application developed by PenCTU will be used for trial management and for recording participant data. Source data will include participants' medical records (e.g. for certain eligibility criteria), participant-completed documents (e.g. informed consent forms), worksheets provided by PenCTU and the eCRF.

In the context of clinical care, investigator site staff must ensure that details of a patient's participation in the trial are recorded in the participant's health record. As a minimum, the health record should be updated to include:

- Consent and eligibility for study
- Dates of all study visits attended
- Dose of trial medication prescribed, and changes
- Changes to concomitant medication
- Adverse events
- Completion or discontinuation of study

18.2. Data handling and record keeping

Electronic data captured in PenCTU's bespoke web-based system will be stored on Microsoft Azure servers located in the UK. The servers are certified to Cyber Essentials PLUS standards. PenCTU staff develop applications in the Azure environment according to the requirements of the UK NHS Health and Social Care Cloud Security - Good Practice Guide.[63]

The eCRF is built in REDCap Cloud. eCRF data is stored in the REDCap Cloud production infrastructure, hosted in Amazon Web Server (AWS) datacentres located in the European Union. AWS datacentres are Service Organization Control (SOC) type 1 and type 2 compliant. Data will be stored on hardware dedicated to REDCap Cloud.

In both systems, all electronic data are backed up and stored with a full audit trail.

18.3. Data quality and completeness

PenCTU Data Management staff will monitor completeness and quality of data recorded in eCRFs and will correspond regularly with site PIs (or their delegated team member) with the aim of capturing any missing data where possible, and ensuring continuous high quality of data. Data quality and completeness checks will be defined by the Data Manager through consultation with the CI, trial statistician, trial manager and other members of the Trial Management Group as required. Checks will be described in the Data Management Plan. Throughout the trial, the Data Manager will report on the quality and completeness of accumulating data to the Trial Management Group.

18.4. Access to data for monitoring and auditing purposes

Direct access to investigator site records will be granted to authorised representatives from the Sponsor (including PenCTU staff) to permit trial-related monitoring, audits and inspections in line with participant consent.

18.5. Archiving

Following completion of trial data analysis, the Sponsor will be responsible for archiving the study data and Trial Master File in a secure location for at least five years after the end of the trial. PenCTU will

prepare the Trial Master File for archiving in accordance with the requirements of the Sponsor's SOP. PenCTU will prepare a copy of the final dataset for archiving according to the requirements of the CTU's SOP.

Principal Investigators at sites will be responsible for archiving Investigator Site Files and trial data generated at the site according to local policy. No trial-related records should be destroyed unless or until the Sponsor gives authorisation to do so. Medical records containing source data or other trial-related information should be labelled, physically or electronically, so as to ensure retention until the Sponsor gives authorisation to destroy. e.g. "Keep until dd/mm/yyyy" (where the date given is five years after the last participant's final visit).

19. TRIAL OVERSIGHT, MONITORING AND AUDIT

19.1. Trial Management Group

A Trial Management Group (TMG) comprising the CI, co-applicants, trial statistician(s), PPI representatives, CTU staff and Sponsor representatives will meet monthly throughout the trial to review overall trial progress, protocol compliance and data quality and completeness, identifying and addressing any issues with trial conduct as they arise.

19.2. Trial Steering Committee

A Trial Steering Committee (TSC) comprising an independent chairperson (clinician), an independent clinician, an independent statistician, PPI representative(s) and designated members of the TMG will meet six monthly throughout the trial to provide overall supervision of a trial on behalf of the Sponsor and funder and to ensure that the trial is conducted in accordance with the protocol and governance guidelines. The full composition, role and function of the TSC will be described in a separate charter. TSC meetings will be guided by progress reports compiled by the TMG in advance of TSC meetings.

19.3. Trial monitoring

In accordance with CTU standard operating procedures for risk assessment and monitoring, a specific monitoring plan will be generated by the CTU, based on the CTU's risk assessment, with input from the TMG. The monitoring plan will be signed off by the CI and Sponsor prior to implementation.

CTU will perform ongoing central monitoring, outputs from which will be discussed by the TMG. Central monitoring will include close supervision of participant recruitment rates, attrition rates, data completeness (missing data), data quality (using range and consistency checks), protocol non-compliance, calendar checks (to identify deviations from participants' visit schedules), consent process checks (through collection of completed de-identified consent forms) and appropriateness of delegated duties at investigator sites (through collection of site delegation logs). Central monitoring will be used to identify areas of potential poor performance at individual investigator sites. Poor performance at sites may trigger on-site monitoring visits (subject to any COVID-restrictions), hosted by the investigator site PI and relevant members of the PI's team. On-site monitoring (if applicable) will be conducted by CTU staff according to established CTU standard operating procedures.

19.4. Audit

Independent audits may be conducted by the trial Sponsor, funder or regulatory bodies. Site PIs, the CI and CTU will permit access to any and all records required by auditors to fulfil their audit duties.

20. ETHICAL AND REGULATORY CONSIDERATIONS

20.1. Research Ethics Committee (REC) review & reports

The Chief Investigator has obtained approval from the Health Research Authority (HRA) and appropriate Research Ethics Committee (REC). The Chief Investigator 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.

20.2. Peer review

The study was funded by Jon Moulton Charity Trust through open competition after independent external peer review was conducted.

20.3. Public and Patient Involvement

PPI input has been provided by seven patients with ArLD and members of the South West Liver Unit patient participation group who have advised on patient-facing aspects of the trial. Representatives will remain actively involved in the study with two each invited to join the TMG and TSC. These patient representatives form an advisory group led by a PPI coordinator to advise on protocol development and study design. They will help tailor the FIT manual to this population and advise on aspects of the qualitative study to guide development of a topic guide. ArLD patients and the PPI group will review all patient-facing written material and be involved in the dissemination of results via their support and local community groups.

20.4. Regulatory compliance

The trial will not commence until a favourable REC opinion and HRA approval has been obtained.

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. For any amendment to the study, the Chief Investigator or designee, in agreement with the Sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

20.5. Protocol compliance

Non-compliance with protocol will be captured on specific non-compliance report forms according to instructions provided by PenCTU and in accordance with PenCTU standard operating procedures. Protocol non-compliance will be reviewed periodically by the Trial Management Group as part of central monitoring (see section 19), with the aim of identifying and addressing recurrent episodes of non-compliance. Each reported non-compliance is reviewed by the PenCTU trial manager. PenCTU staff must immediately inform the PenCTU QA Manager if they believe that a serious breach has occurred (see below). Where the trial manager and/or PenCTU QA Manger believes that a non-compliance might constitute a serious breach, the trial manager should ensure that a completed non-compliance report form is provided to the Sponsor immediately.

20.6. Notification of serious breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety, rights or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial

Where a non-compliance meets the above criteria, PenCTU will immediately notify the CI and Sponsor. The Sponsor will email a serious breach report to the REC and to HRA (using the breaches.nres@nhs.net email address) within seven days of becoming aware of the event.

20.7. Data protection and patient confidentiality

Data will be collected and retained in accordance with the UK Data Protection Act 2018 and the General Data Protection Regulation (GDPR) 2016.The trial Sponsor is the Data Controller for the trial data. PenCTU is a data processor, centrally managing trial data generated at investigator sites. The

University of Plymouth is the data custodian since data are stored on databases managed by the University of Plymouth.

Data including the number of patients screened, approached and interested in taking part will be collected via a log completed by staff conducting screening. Investigator site staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information in accordance with ethics approval.

Any paper-based data collection tools (e.g. worksheets and questionnaires) for capturing source data will remain at investigator sites. Investigator site staff will enter participant data into purposed-designed data capture systems (described in section 18.2). Access to the system for all users (including PenCTU staff) is via a secure password-protected web-interface. Each participant will be allocated a unique system-generated study number. Participants will be identified in all study-related documentation by their study number and initials. Data collected and analysed during the study will be pseudonymised by the use of this unique identifier. A record of trial participants' names and contact details, hospital numbers and assigned trial numbers will be stored securely in a locked room at the trial site and is the responsibility of the site PI.

In order to facilitate central coordination of the study and contact between participants and qualitative researchers, participants' contact details will be entered into the data capture system by investigator site staff (after consent). Only limited staff at PenCTU will have access to these details and these details will not will not be made available in any form to any persons unless needed for study conduct. Datasets prepared for transmission to statisticians (for analysis), co-applicants or Sponsor will be pseudonymised and will not contain any direct identifiers or participant contact details.

Audio data from qualitative interviews will be recorded either via Microsoft Teams or using an encrypted digital audio recorder. Data collected using both Microsoft Teams and encrypted digital recorders will be stored on Microsoft Sharepoint on the University's secure server using the participant's unique study number. All data will be deleted from digital recorders as soon as it is securely transferred. Audio recordings and transcribed data will only be accessible to the qualitative researcher and the CI. Transcription of audio recordings of interviews will only be carried out by members of the research team or professional services with confidentiality agreements in place.

20.8. Financial and other competing interests

The Chief Investigator and TSC committee members will sign a declaration form to disclose any financial or other competing interests including, but not limited to:

- any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
- commercial ties including, but not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

These declaration forms will be filed as part of the Trial Master File.

20.9. Indemnity

This is an NHS-Sponsored research study. If an individual suffers negligent harm as a result of participating in the study, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an *ex-gratia* payment may be considered in the event of a claim.

20.10. Amendments

The Sponsor may make a non-substantial amendment at any time during a trial. If the Sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the Sponsor must submit a valid notice of amendment to the REC for consideration. It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

Amended documents will be allocated a new sequential version number. Once approved by REC, this version will supersede any previous versions.

20.11. Access to the final trial dataset

During the study, the PenCTU data team will have access to the dataset, including identifiable participant data. Other members of the CTU and the wider study team will have restricted access to pseudo-anonymised study data. Access to the dataset will be granted to the Sponsor and host institution on request, to permit study-related monitoring, audits and inspections. Access will be overseen by the CTU data manager and trial manager. Access to the final dataset will be provided to the trial statistician(s) and health economist for analysis.

After the results of the trial have been published, the individual participant data that underlie the results will be available on request from the CI and Sponsor, along with supplementary files as required (e.g. data dictionaries, blank data collection forms, analysis code, etc.). Data will be shared with (or access to the data will be provided to) requestors whose proposed use of the data has been approved by the CI and Sponsor, under an appropriate data sharing agreement. It will not be possible to identify participants personally from any information shared.

21. DISSEMINATION POLICY

21.1. Dissemination policy

The data arising from the trial will be owned by the Sponsor.

On completion of the trial, the data will be analysed and tabulated and a Final Trial Report prepared. This report will be submitted to the Trial Sponsor and Funder and will be accessed on request by contacting PenCTU. Participating investigators will not have rights to publish any of the trial data without the permission of the CI and Sponsor.

The trial will be reported in a manuscript that will be submitted to a peer-reviewed medical journal as open access. The trial will be reported in accordance with the Consort Guidelines. All publications arising from this trial will acknowledge the Funder and a copy of all manuscripts will be provided to the Funder for review at the time of submission to a journal. However, the Funder does not have the right to revise any submission prior to publication. The trial protocol will also be submitted for open access publication to a peer-reviewed journal.

A lay summary of the trial results will be produced and provided to sites, to pass on to trial participants on request.

An anonymised participant level dataset will be produced and held within PenCTU (see section 20.11 for access details).

21.2. Authorship eligibility guidelines and any intended use of professional writers

Authorship of all manuscripts relating to this trial will be determined according to the International Committee of Medical Journal Editors criteria. All members of the TMG who have contributed to trial design, management, analysis and interpretation will be granted authorship of the Final Trial Report. The CI will retain lead author status on the Final Trial Report.

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23. APPENDICES

Appendix 1 – Assessment of capacity to provide informed consent

For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:

- understand the purpose and nature of the research
- understand what the research involves, its benefits (or lack of benefits), risks and burdens
- understand the alternatives to taking part
- be able to retain the information long enough to make an effective decision
- be able to make a free choice
- be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)

Where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected.