

FULL PROTOCOL TITLE:

Informing an assessment pathway for alcohol-related cognitive impairment: A longitudinal study of screening, assessment and prevalence

SHORT STUDY TITLE:

Screening, Assessment and Prevalence of ARCI (SPARCI)

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Chief Investigator:	Prof Thomas Phillips, Centre for Addiction and Mental Health Research (CAMHR)
Co-Investigators:	Prof Judith Cohen, Hull Health Trials Unit & CAMHR Dr Philippa Case, CAMHR
Collaborators:	Prof Colin Drummond, King's College London & CAMHR Prof Simon Coulton, University of Kent & CAMHR Dr Lynsey Corless, Hull University Teaching Hospitals NHS Trust & CAMHR Prof Paolo Deluca, King's College London & CAMHR Prof Cynthia Iglesias, University of York, CAMHR Dr Laura Voss, Humber Teaching NHS Foundation Trust & CAMHR
Sponsor:	University of Hull PVC-Research and Enterprise E-mail: pvc-re@hull.ac.uk
Funder:	National Institute for Health and Care Research: Mental Health Research Groups
Study statistician:	Prof Simon Coulton, University of Kent & CAMHR
Study team:	Sarah Capes (Patient and Public Involvement and Engagement Coordinator, CAMHR) Dimple Lala (Research Assistant) CAMHR

Study Summary

Identifiers	
IRAS Number	369970
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Sponsor Reference No	
Other research reference number(s) (if applicable)	
Full (Scientific) title	Informing an assessment pathway for alcohol-related cognitive impairment: A longitudinal study of screening, assessment and prevalence
Health condition(s) or problem(s) studied	Alcohol use disorder, alcohol-related cognitive impairment
Study Type i.e. Cohort etc	Prospective longitudinal prevalence study
Target sample size	449
STUDY TIMELINES	
Study Duration/length	40 months
Expected Start Date	01/09/2026
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DATA MANAGEMENT	
Data Systems	Hull Health Trials Unit: REDCap Cloud, Box
Data manager	Sarah Sumpter / Deepika Reddy
KEY STUDY CONTACTS	
Chief Investigator	Prof Thomas Phillips – Thomas.phillips@hull.ac.uk
Co-Investigators	Prof Judith Cohen – Judith.cohen@hyms.ac.uk Dr Philippa Case – p.c.case@hull.ac.uk

Protocol Versions

Version stage	Version No.	Version date	Protocol updated & finalised by	Reason(s) for the protocol update
Pre-approval	1.1	07/07/2026	Philippa Case	Following REC advice, the study team will now retain data up to the point of withdrawal and offer participants the option to withdraw from NHS data collection and/or linkage or to continue to allow for this (p.13). Definition for end of study added (p.31).
Pre-approval	1.2	19/08/2026	Philippa Case	Following REC advice the proposed end date and definition have been removed from page 3.
Post-approval	1.3	21/08/2026	Philippa Case	Modification to reflect that only month and year will be collected for the CANTAB rather than date of birth. This will allow us to use the normative data for the cognitive assessments without using identifiable personal data.

DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

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

I (investigator) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:

Signature:



Date: 19/08/2026

Print Name (in full): Thomas Phillips

Position: Professor of Nursing in Addictions

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List of abbreviations

ACT	Alcohol Care Team
APQ	Alcohol Problems Questionnaire
ARCI	Alcohol-Related Cognitive Impairment
AUD	Alcohol Use Disorder
AUDIT	Alcohol Use Disorder Identification Test
CAMHR	Centre for Addiction and Mental Health Research
CANTAB	Cambridge Neuropsychological Test Automated Battery
CIDI-alcohol	Composite International Diagnostic Interview-alcohol section
DSM-5-TR	Diagnostic Statistical Manual (v5) Treatment Version
DSP Toolkit	Data Security & Protection Toolkit
FAST	Fast Alcohol Screening Test
GAD-7	Generalised Anxiety Disorder (7 item)
GDPR	General Data Protection Regulation
HHTU	Hull Health Trials Unit
ICD-11	International Classification of Diseases (v11)
ISC	Independent Steering Committee
LEAG	Lived Experience Advisory Group
MHRG	Mental Health Research Group
MoCA	Montreal Cognitive Assessment
NIHR	National Institute for Health and Care Research
PHQ-9	Patient Health Questionnaire (9 item)
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PPIE	Patient and Public Involvement and Engagement
RCC	REDCap Cloud
REC	Research Ethics Committee
RGF	Research Governance Framework
SADQ	Severity of Alcohol Dependence Questionnaire
SMG	Study Management Group
SOP	Standard Operating Procedure
SPARCI	Screening, assessment and prevalence of alcohol-related cognitive impairment
TLFB28	Timeline Follow Back (28 days)
WHODAS	World Health Organization Disability Assessment Schedule

1. Background

Evidence suggests that a high proportion of people with an alcohol use disorder (AUD) experience cognitive impairment, with estimates ranging from 34% of adults (1) to 48% of adults aged 50+ (2) accessing community treatment for AUD and levels as high as 82% in homeless populations (3). However, accurate prevalence estimates of alcohol-related cognitive impairment (ARCI) are hampered by limited understanding of early indicators, and poor recognition of symptoms, leading to under-identification and subsequent under-recording (4, 5). Whilst there is clear consensus on definitions and assessment of more severe alcohol-related conditions (e.g. alcohol-related dementia (ARD), Wernicke-Korsakoff Syndrome (WKS)) there is a lack of agreement as to the recognition of more subtle cognitive deficits caused by alcohol which require clinical monitoring. In support of this study, we have worked with international experts and the Medical Council on Alcohol to establish clinical consensus regarding the definition and assessment criteria for ARCI that will support this study.

Long-term, heavy alcohol consumption is known to affect cognition through a range of causal pathways, including nutritional deficiencies, hepatological and cerebrovascular disorders, brain injury and direct neurotoxic effects of alcohol (6). For many people, ARCI is transient, with initial improvements seen within 3-8 weeks of abstinence from alcohol (7, 8) and most neuropsychological functions returning to normal range within six months of abstinence (8). However, for some, cognitive impairment is more persistent, including those meeting the diagnostic criteria for dementia due to use of alcohol, Wernicke Korsakoff Syndrome, Korsakoff Syndrome (ICD-11: (9)) or substance-induced major neurocognitive disorder (DSM-5-TR: (10)). Evidence suggests that even with more persistent presentations, the majority of people will experience a stabilisation or improvement in symptoms in the absence of alcohol (7, 11, 12). Therefore, identifying and supporting abstinence in this group is vital.

Alcohol is known to affect short- and long-term memory, executive function (including working memory, impulse control and cognitive flexibility), visuospatial skills, reasoning and attention, as well as leading to problems with social cognition and apathy (6, 13, 14). These may prevent people from being able to access, engage with, and maintain care with specialist alcohol treatment due to a reduced ability to understand, remember and implement clinical advice and through clinical apathy, which may be interpreted as lack of motivation. In addition to the specific difficulties that people with cognitive impairment are likely to encounter with accessing specialist alcohol treatment, current figures suggest that only 18% of people who need alcohol treatment, are in receipt of these services (15). Considering both the lack of access to specialist treatment and the prevalence of coexisting conditions that people with long term heavy alcohol consumption experience (16), people with ARCI are likely to present in other healthcare settings, such as acute hospitals.

Previous studies have demonstrated that alcohol use among acute hospital inpatients has a significant impact on the NHS, through emergency department attendances and urgent care admissions (17). Individuals with alcohol dependence and coexisting physical and mental health conditions utilise hospital services 47% more than similar individuals without alcohol dependence (17), and coexisting mental health diagnoses have been identified as a strong predictor of 30-day alcohol withdrawal hospital readmissions (18). Furthermore, AUD and cognitive impairment have been found to be prevalent in 'hard to discharge' hospital patient populations (19).

Whilst hospitals may not be the best environment in which to give a definitive diagnosis of ARCI, they present the best opportunity to identify the widest range of people at-risk of ARCI. Screening tools are a vital element in identifying people at-risk of ARCI. A recent review of screening tools for ARCI concluded that the Montreal Cognitive Assessment (MoCA) is the best evidenced tool for identifying cognitive impairment in the context of ARCI, but the authors highlighted the need for further evidence and "better

translation of evidence to inform real-world clinical practice” (p.13, (20). The same review emphasised that cognitive screening tools should not replace full neuropsychological testing in the process of diagnosing ARCI and called for more research on defining and diagnosing the condition (20).

In a recent study by Thompson and colleagues (5), the MoCA was administered to ‘high-risk’ patients (defined as having more than three alcohol-related admissions in the past year, or two alcohol-related admissions in any 30-day period, or where the patient or a significant other had concerns about the individual’s cognition) identified by a specialist alcohol team within an acute hospital in the UK (5). They identified cognitive impairment (defined as scoring ≤ 23 on the MoCA) in 36.1% of the high-risk population. In a pilot study led by the University of Hull’s Centre for Addiction and Mental Health Research (CAMHR) group (IRAS 332678), 67% (n=88) of 131 consecutive consenting hospital inpatients with an AUD (defined as scoring ≥ 16 on the AUDIT) scored ≤ 23 on the MoCA, indicating cognitive impairment. Unlike Thompson and colleagues (5), all patients meeting the criterion for AUD were included and participants were not excluded on the basis of receiving sedative medication, which may explain the higher prevalence identified. In the pilot study, 81% of participants had been administered one or more sedative medications in the previous 24 hours (though doses varied significantly) and the average time between admission and assessment was 2 days, meaning that participants were likely to still be acutely unwell.

Whilst acute illness, prescribed medications, recent alcohol consumption and the hospital environment are all likely to affect the results of cognitive testing, these are the reality for clinicians working in hospital environments with people at-risk of cognitive impairment. The studies described tried to take these complexities into consideration by either excluding those on medication or with coexisting conditions likely to impact cognitive assessment (5) or through collecting this information in order to interpret the results (Case et al, *manuscript in preparation*) however, no study has been conducted longitudinally to assess the ability of hospital-based cognitive screening in predicting ARCI as assessed post-discharge and following a period of stabilisation/abstinence to minimise the influence of the hospital environment, acute illness, medications and alcohol intoxication.

Clinical guidelines and evidence reviews (7, 8) indicate that cognitive function stabilises 3 to 6 weeks following abstinence from alcohol and re-assessment of cognitive function has been recommended at 60 days (12, 21). A recent evidence review found that nearly all cognitive function had returned within 6 months for ‘uncomplicated’ cases (i.e. people without more persistent cognitive problems such as those associated with Korsakoff’s Syndrome or dementia due to the use of alcohol) (8). Therefore assessing cognitive function over time to identify whether impairment is related to the hospital environment only, is transient (or time dependent, (13, 22)) and resolves with abstinence or whether impairment is persistent and requires additional assessment and rehabilitation is vital.

Given the need to identify people who may not already be accessing alcohol treatment and to assess people over time in the absence of alcohol, a possible assessment pathway might involve (1) the identification of those at-risk of ARCI through screening in hospital or other frontline services, (2) access for those identified as at-risk to repeated measurement of cognitive function over 6 months to assess whether cognitive impairment is transient or persistent in the absence of alcohol, and (3) a subsequent assessment of ongoing care needs. In reality, many people will struggle to abstain from alcohol over this period of time, yet it is important that assessment of cognitive impairment is not only available to those who abstain. This study seeks to use this proposed pathway to explore the accuracy of the MoCA administered in hospital at T1 (baseline) in predicting ARCI at T2 (4-8weeks), the prevalence of ARCI at T2, and the persistence of ARCI at T3 (6 months), whilst considering the impact of real-world complexities (such as alcohol consumption, alcohol withdrawal and medications) that will

influence this assessment. The results of this study will be disseminated to service users, services and commissioners to inform the future development of an assessment pathway.

Terminology: As noted above, there are multiple causal pathways leading to cognitive impairment in individuals with AUD. Furthermore, alcohol-related causes of cognitive impairment can occur in parallel with non-alcohol-related causes (e.g. early dementia, brain injury). We use the term alcohol-related cognitive impairment (ARCI) throughout this protocol to mean probable ARCI and use this as an umbrella term to incorporate any cognitive impairment that occurs within the context of alcohol use disorder.

2. Aim and research questions

Aim

To understand the course of alcohol-related cognitive impairment (ARCI) amongst recently hospitalised individuals with alcohol use disorder to determine the prevalence and factors associated with ARCI and to inform the development of a diagnostic pathway.

Research questions

- 2.1. What is the predictive value of the Montreal Cognitive Assessment (MoCA) screening tool administered in hospital at T1 (baseline) in identifying people with ARCI at T2 (4-8 weeks post-baseline)?
- 2.2. What is the prevalence of ARCI in recently hospitalised patients with AUD (AUDIT $\geq$ 16), 4-8 weeks post-baseline (T2)?
- 2.3. What proportion of the sample continue to experience ARCI at T3 (6-months post-baseline)?
- 2.4. Which clinical and demographic characteristics are associated with ARCI (T2)?
- 2.5. Which clinical and demographic characteristics are associated with persistent ARCI (T3)?
- 2.6. How do service use and associated costs for people with ARCI (T2) compare to those of people without ARCI?
- 2.7. How do service use and associated costs for people with persistent ARCI (T3) compare to those of people without ARCI?
- 2.8. What proportion of people who consent in hospital attend the follow-up assessments and what factors are associated with attendance at follow-up assessments?

3. Methods:

3.1 Study Design

Prospective longitudinal prevalence study.

3.2 Participants

3.2.1 Pre-Screening Criteria

- Score of Fast Alcohol Screening Test (FAST) $\geq$ 4 or identified by the clinical team as potentially eligible

3.2.2 Inclusion Criteria

- Aged 18+
- Alcohol Use Disorders Identification Test (AUDIT) $\geq$ 16
- Current hospital inpatient

- Has capacity to give informed consent
- Willing and able to participate in the baseline and follow-up assessments
- Speaks English well enough to understand the study and participate in the research assessments or interpreter available and participant speaks one of the languages covered by the cognitive assessments (e.g. Polish, Romanian, Russian)

3.2.3 Exclusion criteria

- Severe and enduring complex co-morbidities which prevent engagement

3.3 Sample size

For objective 1: To assess the accuracy of the Montreal Cognitive Assessment (MoCA) screening tool administered in hospital at T1 (baseline) in identifying people with ARCI at T2 (4-8 weeks post-baseline), a sample size of 269 is required. This sample size calculation is based on a prevalence estimate of 30% (a conservative estimate based on previous research in hospital inpatients (5)) and will allow us to detect a minimum sensitivity of 0.70 and specificity of 0.70.

Based on previous research, we expect 60% of people who consent at T1 (baseline) to complete T2 (4-8 weeks post-baseline) assessments. To account for this expected attrition, we will recruit 449 participants in order to achieve 269 completed assessments at T2 (4-8 weeks post-baseline).

3.4 Recruitment and study flow

3.4.1 Identification

Consecutive hospital inpatients scoring FAST $\geq$ 4 will be invited to participate¹. The care team, including the Alcohol Care Team (ACT), have access to the FAST score of hospital inpatients. A member of the care team will review the list of FAST scores daily to identify patients scoring 4 or more who are potentially eligible for the study. Patients without a FAST score recorded may be identified by a relevant member of the clinical care team as potentially eligible. A member of the clinical care team will make the first approach to potential participants to introduce the study and seek agreement for a researcher to approach them to discuss the study further. Either a member of the clinical care team or the researcher will provide the patient with a participant information sheet (PIS).

Given the need for patients to be medically well enough to be approached, the limited time that people are in hospital and the observational nature of the research, participants can take as long as they wish to consider the project before consenting and will have a minimum of 30 minutes to consider participation. In a previous patient and public involvement (PPI) consultation for a similar hospital-based study for people with alcohol dependence, the group suggested removing or reducing the originally proposed 24hr time limit, indicating that some people would wish to consent and participate on the same day. The period was therefore reduced to 30 minutes, which worked well in that study (IRAS 330296) and a pilot study exploring the prevalence of cognitive impairment amongst hospital inpatients with AUD (IRAS 332678). Whilst this study will be exploring cognitive function and we anticipate some participants will have cognitive impairment, only participants with capacity to give informed consent will be invited to participate in this study and the target population will be similar (IRAS 330296) or the same (IRAS 332678) as previous studies.

¹ A previous study by our research group found that the optimal FAST score to identify those in hospital who experience harmful drinking/possible alcohol dependence (i.e. AUDIT $\geq$ 16) was 3.5 with a sensitivity 0.98, specificity 0.91 and a Youden index 0.89.

3.4.2 Consent

All individuals who have agreed to speak with the researcher will receive a PIS. The researcher will go through the PIS with the individual, describing the aims of the study and what it will involve as well as the screening process. This will be offered to all patients to ensure equity of understanding for people with variable literacy skills. The PIS will inform potential participants that the screening assessment relates to alcohol consumption and problems associated with drinking alcohol in the past 6 months, and that only people meeting a certain score on this questionnaire will go on to participate. The PIS will also include a description of cognitive screening and will explain that it is not a test of intelligence.

The discussion will include the sharing of cognitive assessment scores with the hospital care team. In discussion with the Alcohol Care Team clinicians involved in developing this protocol, and in line with a similar previous study (IRAS 332678), it was decided that the cognitive assessment scores should be shared with the hospital clinical care team who will follow the appropriate clinical care pathway to ensure that (1) patients receive the appropriate care for their needs and (2) non-clinically trained researchers are not put in a position where they have to select which patients need to be referred for further cognitive assessment. If the participant has any concerns about their cognition, they will be sensitively identified to their clinical team. In addition, the PIS contains information on services and sources of information that they can access if needed. The PIS discussion will also include optional consent to access medical records for the current admission and emergency attendance and admission data for the 6 months prior to and following baseline data collection; and an optional consent to provide contact details for one or more locators (key family members and/or friends and/or key healthcare professionals involved in their care) for the purpose of supporting the research team to contact them for follow-up. A mandatory consent field will ask for GP details with an explanation that this is required in case of any serious concerns during follow-up when the individual is no longer under the care of the hospital team. A further optional consent field will request permission to use the individual's NHS number to link routinely collected data across health and care service use. This will enable (pending the appropriate approvals) enrichment of the service use data in the current study or future long-term follow-up.

All patients will be informed that participation is entirely voluntary and their decision not to take part will not affect their care in any way. All patients will be informed of their right to withdraw at any time. Patients will have the opportunity to ask questions and during this discussion, researchers will assess whether the patient has understood the study and is able to make an informed decision about participating. If preferred by the patient and agreed by the clinical care team, this conversation will take place in a confidential area of the ward/hospital/service.

Assessing competence to give informed consent

Whilst this study is exploring the prevalence of cognitive impairment amongst patients with an alcohol use disorder, it is not specifically targeting people with cognitive impairment/suspected cognitive impairment for inclusion. Therefore, the process for assessing competence to give informed consent will follow a similar process to other research studies that have recruited hospital patients with alcohol use disorders (e.g. IRAS 330296, IRAS 275280, IRAS 332678).

This includes the following process:

1. Clinical clearance for participation:

Before researchers approach hospital patients for screening, a member of the hospital team will have assessed they are well enough to participate in the research, including a consideration of the ability to give informed consent.

2. Assessment by researcher that the individual has capacity to give informed consent:

All researchers will be trained to engage potential participants in a consent discussion that allows them to assess whether the individual has understood the study, and has retained the information for long enough to weigh it up and make an informed decision about their participation, and can communicate that decision. To do this, researchers are trained to ask open questions throughout the consent discussion; for example, 'I will be asking questions about your alcohol consumption, your memory and thinking skills, and your health and wellbeing – how do you feel about being asked about these things?' And 'we have spoken a bit about what this research is about and what it will involve. What is your understanding of what this study will involve? / What is your understanding of what this study is about?'

If the researcher has any concerns about the participant's ability to give informed consent, the consent process will be paused, and the researcher will arrange to meet the individual at a different time. They will then seek the advice of the clinical team. Due to the nature of both the conditions for which people are in hospital and the treatment they receive, capacity may fluctuate during the day and/or admission and researchers will work with the clinical team to identify the best time to speak with potential participants. An assessment of capacity to consent will happen at each research visit and ongoing consent will be verbally confirmed at each follow-up meeting. A safety protocol will be in place to ensure that researchers have guidance on how to escalate any concerns and manage immediate risks, both in the hospital environment and during follow-up in the community.

Informed consent to participate will be collected electronically through the data capture system (REDCap Cloud (RCC)). Patients will be provided with a blank copy of the consent form to aid completion of the online form. Participants will keep the blank consent form as a record and, if requested, can have a copy of the signed form mailed to them. Due to the risk of signed consent forms with personal information being left on wards, and due to RCC being a secure online system not set up for printing forms, printed copies of signed consent forms will not be provided at the time of signing.

Inclusion of patients with no or limited English

The RA will go through the PIS with all potential participants, and all data collection will be RA administered ensuring that people with limited written English can be included. We also aim to include individuals with no or limited spoken English. In Hull, the second most commonly spoken language after English is Polish, followed by Romanian (23). As a pragmatic study, we aim to include all patients meeting the study inclusion criteria and most of the cognitive assessments are available in Polish, Romanian and Russian, which were identified as the most commonly spoken languages by our hospital and community alcohol team stakeholders. We will have access to the hospital interpreter services (via telephone) to support with discussing the study, consent and data collection in hospital and community interpreter services for follow-up.

3.4.3 Screening

All participants will be screened for eligibility using the AUDIT (18). The AUDIT (18) will be used to identify people with harmful drinking/possible alcohol dependence (scores of 16-19) or probable dependence (scores of 20 or more) who can be included in the study based on the past 12 months.

An anonymised screening log will be kept of patients who were not eligible to participate in the study, including information on sex, age, ethnicity and reason for non-eligibility. This will enable the research team to track how many people are ineligible to participate due to capacity issues, which could be linked to cognitive impairment and consider the impact of ineligibility due to lack of capacity on prevalence estimates (see analysis section).

3.4.4 Withdrawal of participants

It will be made clear to potential participants that the clinical care that they receive will not be affected by their decision on whether or not to take part in the research and they are free to withdraw at any time without providing a reason for doing so. Any participants withdrawing or deciding not to take part will be thanked for their time. Participants will have the option to have:

- i. Data collected up to the time of withdrawal to be used in analysis – with NHS data and/or linkage used
- ii. Data collected up to the time of withdrawal to be used in analysis – without NHS data and/or linkage used

3.4.5 Baseline data collection (Time 1 – T1)

Following consent to participate, the researcher will invite the participant to continue with data collection. This can happen immediately or after a break if required by the participant. If data collection takes place on a different day, the researcher will go through the study information with the participant again, ensuring that the individual still has capacity to participate and verbally reconfirming consent. Data collection will be led by the researcher and information will be entered directly into RCC. Due to the nature of the hospital environment, data collection can sometimes be interrupted, and individuals may be discharged prior to completing data collection. Should this happen, remaining data can be collected via the telephone.

Characterising the sample

Demographic information will be collected, including age, sex, gender, ethnicity, living situation, Index of Multiple Deprivation (IMD – using postcode) marital status, employment status, veteran status, education level and current/most recent occupation. Health status will be assessed through self-reported long-term conditions and recorded long-term conditions (for consenting participants), smoking/vaping status, and nutritional status (using the Malnutrition Universal Screening Tool (MUST)).

Identifying those at-risk of ARCI

At baseline, the Montreal Cognitive Assessment (MoCA) will be administered to screen for cognitive impairment. Participants will also be asked about previous history of cognitive impairment and concerns about cognition raised by family, friends or professionals.

Interpretation of cognitive assessment

Alcohol withdrawal symptoms will be measured using the Anxiety Sweats and Tremors (AST) assessment. All medications prescribed and taken in the past 24 hours will be collected to calculate an anticholinergic burden (ACB) score to assess the cognitive burden of current medications

Alcohol consumption and drug use from the day of data collection to 28 days previous will be collected via the Timeline Follow Back (TLFB28).

Mental health will be assessed using the Patient Health Questionnaire (PHQ-9) for depressive symptoms and the Generalised Anxiety Disorder scale (GAD-7) for symptoms of anxiety.

Service use and impact

Quality of life will be measured using the EQ-5D-5L. Problems related to alcohol consumption will be collected through the Alcohol Problems Questionnaire (APQ), which examines core domains related to money, friends, legal issues, physical health and mental health.

Self-report data on service use in the past 6 months will be collected. In addition, optional consent will be sought to access data from (i) the current admission to calculate a multimorbidity index and (ii) emergency attendance and admissions in the 6 months prior to and following admission, to explore service use and associated diagnoses.

Please see Table 1 for a summary list of measures and timepoints.

All participants will receive a £15 voucher as a thank you for their time.

3.4.6 Time 2 data collection (T2: 4-8 weeks post baseline)

A follow-up appointment will be arranged either at a hospital, community health or care service, a community setting or at the university. There will also be the possibility of home visits for individuals currently under community services who have been identified by their key worker as appropriate for home visits. Our Lived Experience Advisory Group (LEAG) recommended a proactive approach to engaging with participants following discharge to encourage participation in follow-up. Therefore, the research team will keep in touch regularly with participants through their chosen mode/s of contact (text, email, phone call) to remind them of the study, the details of their follow-up appointment and to enable any appointment changes to be made.

At the appointment, the researcher will go through the study information with the participant again, ensuring that the individual still has capacity to participate and verbally reconfirming consent. The researcher will also verify that the contact details we have for the participant and any locators is up to date. Data collection will be led by the researcher and information will be entered directly into RCC. The setting of data collection will be recorded.

The data collection will include a built-in break with refreshments available. Cognitive measures will take place before the break and all other data collection will take place after the break to minimise the impact of fatigue on cognitive scores. Participants will have the opportunity to take as many other breaks as needed. If needed, some of the data collection can take place over the telephone on a subsequent day. Information on the setting of the data collection will be collected.

Assessing ARCI

There is no gold standard for assessing ARCI; therefore, a reference standard (i.e. the best available method for identifying whether a condition is present (STARD: (24)) based on the ARCI definition and criteria established through the ARCI Consensus delivered in collaboration between the University of Hull and The Medical Council on Alcohol (MCA) has been developed. The ARCI definition requires the presence of (i) cognitive impairment and (ii) alcohol-relatedness with or without (iii) functional impairment. The reference standard will be assessed as follows:

- i. **Cognitive impairment:** assessed using a neuropsychological battery from the Cambridge Neuropsychological Test Automated Battery (CANTAB), including tests of executive function, attention and psychomotor speed, and memory, which are the key cognitive domains affected with ARCI (8, 22, 25-27). In order to compare results with normative data, month and year of birth will be collected.
- ii. **Alcohol-relatedness:** assessed using the baseline (screening) AUDIT, Composite International Diagnostic Interview (CIDI)-alcohol to assess for the presence alcohol dependence and length of time since problems started and the Severity of Alcohol Dependence Questionnaire (SADQ) to determine severity of dependence.
- iii. **Functional impairment:** assessed using the World Health Organization Disability Assessment Schedule (WHODAS 2.0).

The MoCA will be repeated at each timepoint to explore the correlation between CANTAB scores and MoCA score (objective 2 – secondary analysis).

Interpretation of cognitive assessment

Alcohol consumption and drug use from the day of data collection to 28 days previous will be collected via the Timeline Follow Back (TLFB28). A breathalyser will be used to record breath alcohol levels in micrograms of alcohol per 100 millilitres of breath, and the reading will be recorded, unless participants indicate that they do not wish to provide this. The breathalyser will be the last data point collected as our LEAG and stakeholder groups felt that it could have a negative impact for participants if taken too early in the research interview.

Alcohol withdrawal symptoms will be assessed with the Anxiety Sweats and Tremors (AST) assessment. All medications prescribed and routinely taken will be collected to calculate an anticholinergic burden (ACB) score to assess the cognitive burden of current medications.

Service use and impact

Quality of life will be measured using the EQ-5D-5L.

Please see Table 1 for a summary list of measures and timepoints.

All participants will receive a £25 voucher as a thank you for their time, to include local travel expenses. Any additional travel expense needs (e.g. people requiring a taxi) will be arranged on a case-by-case basis.

3.4.7 Time 3 data collection (T3: 6 months post-baseline)

To maximise on engagement with participants at follow-up, a window one month prior to the planned follow-up date and two months post the planned follow-up date will be allowed. A follow-up appointment will be arranged either at a hospital, community health or care service, a community setting or at the university. There will also be the possibility of home visits for individuals currently under community services who have been identified by their key worker as appropriate for home visits. In line with recommendations from our LEAG, participants will be contacted two to four times between T2 and T3 to maintain contact, with additional appointment reminders leading up to the T3 visit.

At the appointment, the researcher will go through the study information with the participant again, ensuring that the individual still has capacity to participate and verbally reconfirming consent. Data collection will be led by the researcher and information will be entered directly into RCC.

The data collection will include a built-in break with refreshments available. Cognitive measures will take place before the break and all other data collection will take place after the break to minimise the impact of fatigue on cognitive scores. Participants will have the opportunity to take as many other breaks as needed. If needed, some of the data collection can take place over the telephone on a subsequent day. The setting of data collection will be recorded.

Assessing ARCI

The reference standard:

- i. **Cognitive impairment:** assessed using a neuropsychological battery from the CANTAB, including tests of executive function, attention and psychomotor speed, and memory, which are the key cognitive domains affected with ARCI (8, 22, 25-27). In order to compare results with normative data, month and year of birth will be collected.

- ii. **Alcohol-relatedness:** assessed using the baseline AUDIT, Composite International Diagnostic Interview (CIDI)-alcohol to assess for the presence alcohol dependence and length of time since problems started and the Severity of Alcohol Dependence Questionnaire (SADQ) to determine severity of dependence.
- iii. **Functional impairment:** assessed using the World Health Organization Disability Assessment Schedule (WHODAS 2.0).

The MoCA will be repeated at each timepoint to explore the correlation between MoCA and CANTAB scores.

Interpretation of cognitive assessment

Alcohol consumption and drug use from the day of data collection to 28 days previous will be collected via the Timeline Follow Back (TLFB28). A breathalyser will be used to record breath alcohol levels in micrograms of alcohol per 100 millilitres of breath, and the reading will be recorded. Alcohol withdrawal symptoms will be collected via the AST. All medications prescribed and routinely taken will be collected to calculate an anticholinergic burden (ACB) score to assess at the cognitive burden of current medications.

Service use and impact

Quality of life will be measured using the EQ-5D-5L. Problems related to alcohol consumption will be collected through the Alcohol Problems Questionnaire (APQ), which examines core domains related to money, friends, legal issues, physical health and mental health.

Self-report data on service use in the past 6 months will be collected. In addition, service data including emergency attendance and admissions in the 6 months prior to and following admission will be collected for participants who provide optional consent for this.

Please see Table 1 for a summary list of measures and timepoints.

All participants will receive a £25 voucher as a thank you for their time, to include local travel expenses. Any additional travel expense needs (e.g. people requiring a taxi) will be arranged on a case-by-case basis.

Table 1: Summary table of measures and timepoints

Assessment	Duration (mins)	Screening	Baseline (T1)	4-8 wks post BL (T2)	6 months post BL (T3)
Characterising the sample					
Demographic information: age, sex, gender, ethnicity, living situation, marital status, employment status, veteran status, education level, occupation	5		X		
Health status: smoking/vaping	<1		X		
Health status: malnutrition risk	2		X		
Health status: Self-reported long-term conditions	1		X		
Assessing ARCI					
Cognition: MoCA	10		X	X	X
Cognition: Reference standard ARCI assessment				X	X
- Cognition: CANTAB tests	60				
- Alcohol: CIDI, SADQ	10				
- Functioning: WHODAS 2.0	5				
Cognition:					
- Concerns raised by family or professionals	1		X		
- Medical history: cognitive impairment	2				
Interpreting the cognitive assessment					
Medications (ACB score)	1		X	X	X
Breathalyser	1			X	X
AST	1		X	X	X
Alcohol: AUDIT	2	X			
Alcohol: TLFB28 (start with day of assessment)	10		X	X	X
Drugs: TLFB28 (start with day of assessment)	1-5		X	X	X
Alcohol: APQ (Core domains only, 23 items)	3		X		X
Mental Health: PHQ-9	2		X		
Mental Health: GAD-7	2		X		
Service use and impact					
QoL: EQ-5D-5L	2		X	X	X
Service: past 6 months	5		X		X
Total time:		2	53	106	113

SCREENING, ASSESSMENT AND PREVALENCE OF ARCI (SPARCI): A LONGITUDINAL STUDY



PRE SCREENING

Hospital inpatients scoring **FAST $\geq$ 4** or identified by the clinical team as potentially eligible will be invited to participate.



SCREENING

Individuals agreeing to speak to the researcher will be given **PIS** and informed that **only those meeting the score criteria will proceed**.

- Those who consent will complete AUDIT.
- Participants **scoring $\geq$ 16 on AUDIT** will be invited to complete baseline measures.



T1: BASELINE

Data collected immediately or on a later day as per participant.

1

- **Demographics**
- **Cognition** - MoCA and asking about prior cognitive impairment and concerns from family, friends, or professionals.
- **Alcohol measure** - APQ & TLFB28
- **Alcohol withdrawal**
- **LT Conditions**
- **MUST**
- **Cognitive Burden of medications**
- **Mental health**
- **QoL**
- **Service Use**



T2: 4-8 WEEKS POST-BASELINE

Participants will be seen in either hospital or community.

2

- **MoCA**
- **Reference Standard** - Cognition (CANTAB), Alcohol (CIDI & SADQ) and Functional Impairment (WHODAS 2.0)
- **TLFB28, Alcohol Withdrawal, Breathalyser**
- **Cognitive Burden of medications**
- **QoL**



T3: 6 MONTHS POST BASELINE

Participants will be seen in either hospital or community.

3

- **MoCA**
- **Reference Standard** - Cognition (CANTAB), Alcohol (CIDI & SADQ) and Functional Impairment (WHODAS 2.0)
- **TLFB28, Alcohol Withdrawal, Breathalyser**
- **Cognitive Burden of medications**
- **QoL**
- **Service use**

Figure 1: Study flow diagram

3.5 Measures

3.5.1 Screening

All participants will be screened for eligibility using the AUDIT (Alcohol Use Disorders Identification Test) (28), which quantifies alcohol misuse and comprises 10 questions. It was developed by the World Health Organization (WHO) as a simple method of screening for risky drinking and to assist in brief assessment. It is used to help identify alcohol dependence and some specific consequences of harmful drinking and is designed for use by health care practitioners. The AUDIT (28) will be used to identify people with harmful/possible alcohol dependence (scores of 16-19) or probable dependence (scores of 20 or more) who can be included in the study based on the past 12 months. It will also be considered as part of the identification of ARCI (under the criterion “alcohol-relatedness” as this the most likely tool to be used in clinical practice for this purpose).

3.5.2 Assessing ARCI

Montreal Cognitive Assessment (MoCA)

The MoCA is a 30-item assessment for identifying cognitive impairment, especially at an early stage of impairment (29). The maximum score is 30, with a higher score indicating better cognitive function. The cut points for the MoCA in general populations (30) are:

- 26 or above: normal cognitive performance
- 18-25: mild cognitive impairment
- 10-17: moderate impairment
- 0-9: severe impairment

The MoCA is the best evidenced cognitive screening tool in populations with ARCI (20). Validation studies have indicated optimal cut scores in ARCI populations of ≤ 24 in ARCI populations without Korsakoff's Syndrome (31) and ≤ 23 in populations with Korsakoff's Syndrome (31, 32). A cut score of ≤ 23 has been used in pilot work conducted by this research group and in other research in this area (5). The MoCA has three versions (v8.1, v8.2, v8.3) with slightly different questions; a different version will be used at each timepoint to reduce repeated measures bias.

ARCI reference standard:

The definitional criteria for ARCI were developed through consensus process delivered in partnership between the Centre for Addiction and Mental Health Research (CAMHR) and the Medical Council on Alcohol (MCA) with experts from the fields of neuropsychiatry, neuropsychology, addiction psychiatry, liaison psychiatry, hepatology, old age psychiatry, ARCI and an expert by experience. To meet the criteria, individuals must have (i) cognitive impairment and (ii) alcohol-relatedness with or without (iii) functional impairment. The reference standard will be assessed as follows:

- i. **Cognitive impairment:** assessed using a neuropsychological battery from the CANTAB ([Digital cognitive assessments - Cambridge Cognition](#)), including tests of executive function, attention and psychomotor speed, and memory, which are the key cognitive domains affected with ARCI (8, 22, 25-27). CANTAB is a validated touch screen computer-based cognitive assessment battery with subtests based on traditional paper neuropsychological tests. It is available in multiple languages, can be delivered by researchers and has been used in a wealth of research including studies examining cognition deficits in people with AUD (25-27, 33-37). The complete battery will last for a maximum of 1 hour. The order of the MoCA and CANTAB battery will be randomised to reduce order effects. In order to compare results with normative data, month and year of birth will be collected.

- ii. **Alcohol-relatedness:** assessed using the AUDIT (above), Composite International Diagnostic Interview (CIDI)-alcohol and the Severity of Alcohol Dependence Questionnaire (SADQ). The CIDI (38) has been developed and validated to assess mental health disorders internationally. It includes a substance use disorder module and only the alcohol questions will be included in this study. A score of 3 or more indicates alcohol dependence, though not all questions score equally. The SADQ is a 20-item questionnaire containing items representing five domains of the alcohol dependence syndrome: (i) physical withdrawal signs (ii) psychological withdrawal signs (iii) withdrawal relief drinking (iv) tolerance (v) reinstatement following a period of abstinence (39).
- iii. **Functional impairment:** assessed using the World Health Organization Disability Assessment Schedule (WHODAS 2.0). The WHODAS 2.0 (40) is a tool developed to assess function in six domains: cognition, mobility, self-care, getting along, life activities, and participation. It is recommended for functional assessment within the DSM-V (10). We will use the 12-item interviewer-administered version of WHODAS 2.0.

Cognition medical history

At baseline, participants will be asked about previous history of cognitive impairment and associated conditions (e.g. traumatic brain injury, dementia) and current status.

Concerns about cognition raised by family, friends or professionals will be ascertained through the following question:

“Has a relative or friend, doctor or other health worker been concerned about your cognition (e.g. your memory, concentration or other thinking skills) or suggested you access help for this?”

If yes, “was this in the last year or more than one year ago?”

3.5.3 Interpreting cognitive assessments

Alcohol withdrawal symptoms

The Anxiety Sweats and Tremors (AST) assessment (41) will be administered to assess for withdrawal symptoms to inform the interpretation of cognitive screening results. The AST is a brief 3-item measure assessing the three core elements of alcohol withdrawal: anxiety, sweats and tremors, and has shown good internal consistency and reliability (41).

Medications

All medications prescribed and routinely taken will be collected to calculate an anticholinergic burden (ACB) score to assess at the cognitive burden of current medications (e.g. [ACB Calculator](#)).

Alcohol consumption and drug use

Alcohol consumption and drug use from the day of data collection to 28 days previous will be collected via the Timeline Follow Back (TLFB28) (42). Collecting data on alcohol consumption on the day of data collection will allow the research team to account for the impact of alcohol consumption on cognitive scores, whilst data on the previous 28 days will allow the team to characterise participants in terms of their recovery, due to length of abstinence being important in terms of expected cognitive function. Whilst a period of abstinence is preferred in advance of assessing cognitive function, continued alcohol consumption should not prevent assessment, and this study aims to reflect what will happen in practice to provide practical and applicable findings for clinical settings.

A breathalyser reading will also be collected and recorded as an objective measure of recent alcohol consumption.

3.5.4 Characterising the sample

Information will be collected on age, sex, gender, ethnicity, marital status (single, married/civil partnership, widowed, divorced/separated), living situation (number of adults, number of children (under 16), relationship to other household members and type of accommodation), employment status (has paid work - F/T (30+ hours per week)/ has paid work - P/T (8-29 hours per week)/ has paid work - P/T (under 8 hours per week)/ unemployed/economically inactive/retired/student; veteran status; postcode (for Index of Multiple Deprivation and access to services). Education level and current or most recent occupational classification will be collected and grouped in line with Office for National Statistics (ONS) UK classifications.

Long-term conditions and coexisting conditions

Participants will be asked: ‘Do you have any physical or mental health conditions or illnesses lasting or expected to last 12 months or more?’ If participants answer ‘yes’, they will be able to list up to six conditions. Anyone listing a condition will be asked: “Does this condition reduce your ability to carry out day-to-day activities?” In line with the Health Survey for England methodology (43), these will be coded into conditions and ICD-10 chapter categories.

In addition, optional consent will be sought to access data from the current admission including data on all diagnoses recorded within the admission. Diagnosis data will be used to calculate a multimorbidity index.

Smoking status

Smoking status: currently smoking (daily or non-daily), quit within the past year, quit more than one year ago, never smoked, or if use of non-cigarette tobacco (e.g. cigar/pipe smoking) will be collected (44).

Vaping status: current, past, never.

Nutrition: Malnutrition Universal Screening Tool (MUST)(45)

MUST is a 5-step screening tool to identify adults who are malnourished, at-risk of malnourishment or obese. It includes an assessment of Body Mass Index (BMI) (with alternative measures if this is not possible), unplanned weight loss, and acute disease effect to score patients as:

- 0 – low risk
- 1 – medium risk
- 2 or more – high risk

Patient Health Questionnaire (PHQ-9 (46))

The 9-item Patient Health Questionnaire is a commonly used tool for the identification and assessment of depressive disorders in primary care and medical settings (47). Each of the 9 items represent depressive symptoms and are scored 0 (*not at all*), to 3 (*nearly every day*) with total questionnaire scores representing:

- 5-9: mild depressive symptoms
- 10-14: moderate depressive symptoms
- 15-19: moderately severe depressive symptoms
- 20-27: severe depressive symptoms

Generalised Anxiety Disorder scale (GAD-7 (48))

The 7- item Generalised Anxiety Disorder (GAD-7) questionnaire is calculated using a Likert scale of 0 (*not at all*) to 3 (*nearly every day*) in response to each question. With a maximum score of 21, scores representing:

- 5: mild anxiety
- 10: moderate anxiety
- 15: severe anxiety

Additionally, the GAD-7 can be used to screen for panic disorder, social anxiety disorder and post-traumatic stress disorder.

3.5.5 Service use and impact

Participants will be asked to report their service use in the past 6 months using a Client Service Receipt Inventory (CSRI). This study will use a version of the tool based on previous research in this area (IRAS: 332678) and will be used to capture data on the participants' use of specialist alcohol treatment, acute, community, mental health, primary care, social service and criminal justice use over the past 6 months.

In addition, optional consent will be sought to access data from (i) the current admission at the time of recruitment and (ii) emergency attendance and admissions in the 6 months prior to and following admission, allowing us to look at hospital data for people who did / did not complete follow-up assessments.

Further optional consent will be sought for permission to use the individual's NHS number to link routinely collected data across health and care service use. This will enable (pending the appropriate approvals) enrichment of the service use data in the current study or future long-term follow-up.

EQ-5D - five domain and five level (EQ-SD-5L, (49))

The EQ-5D-5L is a generic health-related quality of life tool aimed at the general population, comprising five questions each with five levels of response. It represents an improvement upon the properties of the EQ-5D-3L as it allows for greater sensitivity/responsiveness, thus, addressing the issue of ceiling and floor effects. We will rely on the crosswalk value sets for the UK available from the EuroQoL Group at <https://euroqol.org>.

Alcohol Problems Questionnaire (APQ (50, 51)):

The APQ is a 44-item questionnaire assessing potential problems with psychological, physical, social, legal, employment, relationships and parenting that may be experienced due to alcohol. The APQ is split into the sections: common scale (friends, finance, legal, physical, affective), and three sub-scales dependant on circumstances marital, children and work, with only the common scale administered to everyone and the other sections only administered where relevant. For this research study, only the common scale (applicable to everyone) will be administered.

3.6 Analysis

- 3.6.1 What is the predictive value of the Montreal Cognitive Assessment (MoCA) screening tool administered in hospital at T1 (baseline) in identifying people with ARCI (assessed using diagnostic criteria developed through expert consensus) at T2 (4-8 weeks post-baseline)?

ARCI status is categorised as a dichotomous outcome, ARCI positive or ARCI negative. We will construct a Receiver Operating Characteristic (ROC curve) plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) for all thresholds of the MoCA screening tool at T1. An initial examination of the Area Under the Curve (AUC) will be made. An AUC below 0.5 would suggest the MoCA has no discriminant properties, >0.5 to <0.7 would suggest the MoCA has very limited clinical utility as a screening tool. If the AUC is 0.7 or above, we will establish the cut-point that maximises sensitivity and specificity using the Youden's index. We will report sensitivity, specificity, positive and negative predictive value and associated 95% confidence intervals.

To explore the role of missing data in the analysis and how it may be associated with ARCI status we will undertake two additional analyses. First using an assumption that missing ARCI status is missing at random (MAR). We will conduct a multiple imputation, deriving models that predict ARCI status and combining them to predict the probability of a missing outcome was ARCI positive or negative. A sensitivity analysis will be conducted to explore the impact of missing at random data on the results observed. A second missing data analysis will be made under the assumption that the data is missing not at random (MNAR). In this analysis we will employ a pattern mixture model using a sequence of assumptions regarding the pattern of missing data and explore the impact of the data being MNAR using a sensitivity analysis.

In order to explore the impact of key demographic (sex, ethnicity and age) and clinical (alcohol consumption, alcohol withdrawal, medication) characteristics on cut-points for MoCA a ROC regression analysis will be conducted.

As ARCI status could be categorised as normal, mild, moderate and severe we will conduct a secondary analysis to explore AUC, sensitivity, specificity and positive and negative predictive value at different cut-points for different levels of ARCI status. As this analysis is exploratory no adjustment for missing data will be employed.

The primary analysis will be repeated to explore the predictive value of MoCA for persistent ARCI at T3.

Secondary analyses will explore the correlation between MoCA score and CANTAB scores at each timepoint.

3.6.2 What is the prevalence of ARCI in recently hospitalised patients with AUD (AUDIT≥16), 4-8 weeks post-baseline (T2)?

The prevalence of ARCI amongst hospital patients with AUD 4-8 weeks post baseline and associated measures of precision will be calculated as the proportion of people testing positive for ARCI using the reference standard assessment.

Pattern-matching techniques will be used to explore the impact of missing data in the form of: i) patients with AUD who lacked capacity to consent to participation and ii) participants lost to follow-up, on prevalence estimates.

Secondary exploratory analyses of cognitive data from the CANTAB will examine patterns and severity of cognitive deficits.

3.6.3 What proportion of the sample continue to experience ARCI at T3 (6 months post-baseline)?

The prevalence of ARCI amongst hospital patients with AUD 6-months post-baseline and associated measures of precision will be calculated as the proportion of people testing positive for ARCI using the reference standard assessment.

3.6.4 Which clinical and demographic characteristics are associated with ARCI (T2)?

The relationship between clinical and demographic characteristics at baseline (T1) and ARCI (T2) will be explored using ridge regression for logistic regression models. Ridge regression is an L2 regularisation model, which corrects for multicollinearity where multiple variables may be measuring the same underlying construct (52).

3.6.5 Which clinical and demographic characteristics are associated with persistent ARCI (T3)?

The relationship between clinical and demographic characteristics at baseline (T1) and persistent ARCI (T3) will be explored using ridge regression for logistic regression models (52).

3.6.6 How do service use and associated costs for people with ARCI (T2) compare to those people without ARCI?

Service costs will be estimated using PSSRU reference costs ([Unit Costs 2022-2027 - Care and Outcomes Research Centre](#)) and NHS reference costs ([NHS England » National Cost Collection for the NHS](#)).

Mean costs will be estimated per service type and across all services for 1) the 6-months pre-baseline and 2) the 6 months post-baseline and will be compared between those with and without ARCI at T2, using analysis of covariance (ANCOVA) with post-discharge service use as the dependent variable, ARCI positive / ARCI negative (T2) as the grouping variable and pre-admission service costs as the covariate. Data will be bootstrapped with a minimum of 1000 samples to account for the non-normal distribution of service data.

3.6.7 How do service use and associated costs for people with persistent ARCI (T3) compare to those people without ARCI?

Service costs will be estimated using PSSRU reference costs ([Unit Costs 2022-2027 - Care and Outcomes Research Centre](#)) and NHS reference costs ([NHS England » National Cost Collection for the NHS](#)).

Mean costs will be estimated per service type and across all services for 1) the 6-months pre-baseline and 2) the 6 months post-baseline and will be compared between those with and without ARCI at T3, using analysis of covariance (ANCOVA) with post-discharge service use as the dependent variable, persistent ARCI positive / persistent ARCI negative (T3) as the grouping variable and pre-admission service costs as the covariate. Data will be bootstrapped with a minimum of 1000 samples to account for the non-normal distribution of service data.

3.6.8 What proportion of people who consent in hospital attend the follow-up assessments and what factors are associated with attendance at follow-up?

Completed follow-up assessments at T2 and T3 will be calculated as a proportion of the total number of participants consenting and completing baseline data collection.

A prognostic model using regression analysis will be developed to identify which demographic and clinical characteristics and/or pattern of service use are associated with attendance at follow-up appointments.

A detailed statistical analysis plan and published protocol will be finalised prior to analysis commencing.

Data Review

At regular intervals during the recruitment phase the recruitment pattern will be examined and adjustments made to the recruitment process if required.

4. Storage and handling of data and confidentiality

4.1 Data management

A data management plan agreed by the Chief Investigator, Sponsor, Hull Health Trials Unit (HHTU) and statistician will be drafted to provide detailed instructions and guidance relevant to database set-up, data entry, validation, review, query generation and resolution, quality control processes involving data access and transfer of data to the sponsor at the end of the study and archiving.

All the information obtained about participants in the course of the study is confidential and will be held in accordance with the General Data Protection Regulation (GDPR 2018). Data will be entered into RedCap Cloud (RCC), a web-based electronic data capture system. The HHTU Information Systems team will work with the Chief Investigator to design the specification, build and validate the database, which will meet the required regulatory standards. Data are stored on dedicated RCC hardware in EU data centres (including real-time backup) managed by Amazon Web Services to industry standards outlined in ISO 27001, PCI DSS, FISMA, CIS, CSA, NIST and UK Cloud Security Principles. Data are encrypted at rest and in transit. RCC delivers compliance to HIPAA, CFR Part 11 and EMEA Annex 11.

CANTAB is a product developed by Cambridge Cognition. As an ISO 27001 certified company, Cambridge Cognition always ensures the highest levels of data security. All CANTAB study data is synchronised between devices and centralised through secure cloud servers. They keep data secure by: Encrypting data at rest, using HTTPS encryption for all data transfers, only permitting authorised users access to study data and use of secure servers in HIPAA/GDPR compliant private cloud.

HHTU use Box.com for collaborative cloud file storage. The HHTU Box instance is managed by HHTU with access limited to HHTU staff and authorised members of the research team. Box uses EU data centres and complies with (and is independently audited against) the following standards: SOC 1, SOC 2 and SOC 3, ISO27001/270018, Department of Defence Cloud computing Security Requirements Guide, FedRAMP Level 4, FISMA, FINRA/SEC 17a-4, HIPAA/HITECH

Box acts as a data processor only for the purposes of storage of study data. Further details on Box data security and GDPR compliance is available here: <https://www.box.com/n-gb/security>. The data protection risks of HHTU's use of Box have been formally evaluated via a data protection impact assessment.

For all participants, the personal data collected in this study will be the participant's name on the electronic informed consent form, their postcode and their contact details. If the participant provides consent for researchers to collect data from their hospital medical records and linkage to routinely collected data, their NHS number will be stored on the RCC database. Personal identifiers are labelled in the study database and will be excluded from all study data downloads including the final analysis dataset. Participant data will be linked to a unique study number for the purposes of data analysis; however, no one outside the study and usual care team will be able to identify the participant from this number.

Only authorised study team staff will have access to the data collected in this study. However, they may be looked at by representatives of regulatory authorities and by authorised people from the University of Hull and HHTU to check that the study is being carried out correctly. All will have a duty of confidentiality to research participants to protect their data.

Access to the RCC database will be managed by HHTU staff who will create users on behalf of the study team. Users will be required to complete RCC training and sign a terms of use document. Users are granted role-based access.

The database will be 'locked' to obtain the final dataset after:

- Study completion (last patient, last visit)
- Completion of coding and data entry
- All data queries resolved, and the database updated
- Study team notified of data lock

Following data lock, data will be exported from the study database in the required formats for analysis, long-term storage and sharing. The trial dataset will be exported from RCC for analysis and stored in HHTU Box Instance with restricted access to authorised research staff for the purposes of reporting and statistical analysis. HHTU SOPs will be followed for the process of database lock and export including pseudo-anonymisation. HHTU will ensure no direct participant identifiers are present in any exported datasets.

An end of study notification will be sent to the sponsor before data is released via the University of Hull Box instance to the study statistician at the University of Kent, Canterbury, UK for the completion of the statistical analysis. A copy of the final study dataset will also be archived by HHTU on behalf of the Chief Investigator and sponsor who are all part of the University of Hull. Other authorised researchers requesting access to the dataset for further research may apply through the CI. Applications will be considered in keeping with the data sharing policy which will be put in place before the end of the study.

4.2 Confidentiality

All information collected during the course of the study will be kept strictly confidential. All study staff and investigators will comply with the principles of the Data Protection Act 2018 and with all aspects of GDPR 2018 in protecting the rights of study participants with regards to the collection, storage, processing and disclosure of personal information. Information will be held securely electronically at HHTU.

Each participant will be assigned a unique study ID number which will be used for all information entered into the electronic RCC database. All data electronically held by the HHTU, will be stored within systems in scope of the HHTU NHS Data Security and Protection Toolkit. HHTU Data Management Team will control access permissions to the RCC database and Box throughout the study and afterwards when the documents have been archived. Access permission will be granted based on delegated study role and level of access required, e.g. editor or read only. Access will be revoked when staff leave the study or after Data Lock.

Any personal data held physically at participating sites will be stored according to local NHS policy. Any physical data held by the HHTU will be stored within a locked filing cabinet within the secure archive room which has restricted and auditable access controls.

Data generated as a result of this study will be available for inspection on request. Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

No participant identifiers will be included in any publications or dissemination activities arising from this work.

5. Data Monitoring

The monitoring of data quality and completeness will be undertaken by the study team and HHTU according to the monitoring plan.

During the first days of recruitment and data collection, there will be more frequent monitoring of informed consent forms and study measures to ensure that researchers are conducting the study in accordance with the protocol. There will be ongoing remote and in-person monitoring of informed consent and study measures throughout the recruitment period.

Electronic data systems will prompt when follow-up data collection is due, and researchers will mark as complete or confirm as unavailable if unable to contact participants within the times stated in the protocol. Collection of hospital admission outcome information from hospital records for participants who give consent may be conducted at a later date when the outcome of the admission has been documented. HHTU will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the HHTU to ensure the quality of data collection.

6. Safety Procedures and Reporting

6.1 Safety Procedures

This is a non-interventional study with regards to the care received by the participants, and as such there is no requirement for reporting clinical adverse events.

The main safety concerns within the study relate to researchers working within hospital settings conducting baseline interviews and, in the community, conducting 6-month follow-up interviews, recruiting participants with an unknown history of risks. As with all interactions with the general public, appropriate safeguards will be in place to account for potential risks to researchers. Participants may present with changeable behaviour due to levels of pain, mental health issues, distressing circumstances, or alcohol and/or drug use/withdrawal. Predicting an individual's behaviour is difficult. The following actions will be taken to mitigate risks and reduce the potential for harm to research workers.

Firstly, protecting the health and safety of the researchers is paramount. All researchers will be employed by the University of Hull and will possess an Honorary Contract with the relevant NHS Trust, which will allow them to be orientated to the hospital at the start of their employment. These arrangements will ensure all researchers receive the relevant safety and risk training and lone working policies.

Baseline Recruitment:

All researchers trained to deliver the study will have experience of working within health care settings or of recruiting participants from these or similar settings. Visits to the hospital sites prior to the study recruitment period will identify policies and procedures for emergency events including fire and

violence, comfort areas for researchers (i.e. identifying where to obtain food/drinks and access to toilets) and points of contact with clinical staff will be identified.

Researcher training will incorporate precautions to minimise risks, including the following practical issues:

1. Training and monitoring of the appropriate cleaning of research equipment (computer tablets) in accordance with Trust infection control policies.
2. Researchers will identify who the responsible clinical team leader is on each shift over the study recruitment period.
3. Researchers will introduce themselves to the clinical team to remind staff of their presence.
4. Researchers will know how to obtain clinical approval to approach potential participants.
5. Researchers will inform appropriate clinical staff of their whereabouts, specifically when they are undertaking study recruitment.
6. Researchers will identify a dedicated research room/cubicle where recruitment will be conducted (where applicable) and will assess the layout of the room and identify the nearest exit. Where possible, room exits should not be impeded and researchers should not place the participant between themselves and the exit.
7. Researchers will wear agreed ID with the appropriate safety breakaway lanyard and will dress appropriately for the environment.
8. Researchers will terminate the interview early if feeling threatened.
9. Researchers will notify appropriate clinical staff once they have completed a participant interview.
10. Researchers will report all incidents or concerns to the identified clinical team leader.
11. Researchers will inform the study team of any incidents or concerns they may have.

Follow-up Interviews:

All researchers will be trained on the lone working policy and will predominantly arrange follow-up interviews in agreed clinical settings (i.e. hospital site outpatient department) or public spaces. Where the participant is under a community health or care service, the participant has consented to the researcher contacting this person, and the worker has confirmed that a risk assessment has been conducted and home visits are appropriate, the follow-up visit may be conducted at home, following the lone worker policy. There is the possibility of assessments being conducted over the phone or via video call in some circumstances. In accordance with the lone working policy there are clear procedures for notifying the study team supervisor based at the University of Hull when a planned interview is taking place and once when it has been completed.

7. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

7.1 Quality Assurance

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP) and the NHS Research Governance Framework (RGF), and through adherence to HHTU Standard Operating Procedures (SOPs).

A Study Management Group (SMG) will meet every month to discuss study progress against milestones and consider any action required. The SMG will report into the Independent Steering Group (ISG) for the NIHR Mental Health Research Group.

7.2 Patient and Public Involvement

The Centre for Addiction and Mental Health Research employs two full time Patient and Public Involvement and Engagement (PPIE) Coordinators, one of whom supports the involvement of people with lived experience in contributing to our work around alcohol-related cognitive impairment. We have a Lived Experience Advisory Group (LEAG) dedicated to research on ARCI and the LEAG has assisted in the development of a) the design and content of the PIS and other participant study documents, b) the practical implementation of the study in hospital/follow-up; c) the researcher training requirements; and d) the delivery of the study survey measures. Key changes to the protocol following input from our LEAG are included throughout the protocol and include (1) the time to consider participation, (2) the inclusion and timing of the breathalyser and (3) the assertiveness with which researcher should engage with participants following discharge. The LEAG were also consulted on engaging with locators to facilitate contact post-discharge if we are unable to reach participants and due to concerns about vulnerable individuals, we have added check-ins at follow-up points to ensure that participants are still happy for us to contact their named locators and to check contact details. Based on feedback from the LEAG, various changes have been made to the PIS to improve readability, including the addition of a visual aid. The LEAG felt that it was important to use the term alcohol-related cognitive impairment because this is the phrase used in the programme of research, provided that clear explanations of the term were given. The LEAG will be consulted on relevant study modifications and dissemination of findings.

7.3 Ethics Committee Approvals

The study shall not commence until ethical approval has been obtained from the NHS Research Ethics Committee and Health Research Authority.

The Sponsor (University of Hull) will be responsible for deciding whether modifications are substantial, minor or are modifications of an important detail, in collaboration with the Chief Investigator. Where a modification is required to study documentation that required Research Ethics Committee (REC) approval, changes will not be implemented until REC approval and HRA categorisation is received. Where a modification requires local approval, this shall be sought prior to the modification being implemented in accordance with the categorisation given on the HRA approval letter. Should a modification be required to eliminate an apparent immediate hazard to participants this may be implemented immediately and the REC/HRA and R&D will be notified as soon as possible. Minor modifications for logistical or administrative purposes may be implemented immediately. Modifications of important details will be assessed for any required approval prior to implementation in collaboration with the Sponsor. Modifications will be logged on the Sponsor Study Modification Log and stored in the Study Master File. A final report will be submitted to the REC within one year after the end of the study.

7.4 Ethical Considerations

The study team have identified the following ethical considerations in developing the study methodology:

Approaching potential participants with sensitivity and consideration: Potential participants will be given time between their admission and the initial approach by a researcher and will be given time to consider the PIS and study information provided. Researchers will ensure that patients know participation is entirely voluntary. A researcher manual and training will be developed which will include

details of how to sensitively approach and speak with patients and how to identify if people are becoming upset and what to do.

Study questionnaires: There may be some psychological discomfort resulting from completion of the study specific questionnaires and interviews, for example, regarding alcohol habits and associated problems. If participants become upset during the research interview, they will be able to take a break and will be given the opportunity to stop entirely. Researchers will be trained to respond sensitively to patients who become distressed. For the baseline assessment, all participants will be inpatients and the ward staff will be aware of their participation in the research and able to offer additional support if needed. For the follow-up assessments, most participants will be community-based and may not have access to services, therefore a safety protocol will be followed and any participants requiring additional support will be provided with a list of services (developed in conjunction with research sites) where people can access support locally. The researcher manual will also consider follow-up issues, such as proactively discussing the option to withdraw, and how to speak with people who have recommenced alcohol consumption between the baseline and follow-up interviews in order to collect accurate data whilst being sensitive to the participant's situation.

Honorarium: All participants will be given £15 voucher to compensate them for their time at baseline and £25 to compensate them for their time at each follow-up appointment.

Language barriers: The study team aim to include people whose primary language is one of the key languages spoken in the local area (Polish, Romanian, Russian). The MoCA is available in all three languages and most subtests from the CANTAB are also available in these languages. Interpreters are available via a telephone service in the hospital, and we will employ a similar service in the community. This process will enable non-English speakers from key local communities to participate, and will enable us to understand some of the challenges and needs of our local population when considering an assessment pathway for ARCI.

Anonymised data and confidentiality: No research data collected in the study will be attributed to a named individual or their medical records. Only MoCA scores collected in the hospital will be communicated or transferred to clinical staff or the participant's medical record. No other data collected will be shared.

Any significant and immediate concerns identified during hospital-based recruitment will be highlighted to the Clinical Lead. Any significant and immediate concerns identified during follow-up interviews will be raised with the CI and communicated to the participant GP with local procedures being followed for acute mental health and physical health concerns (i.e. presentation to Emergency Department). Consent to contact the GP for this reason will be sought during the consent process.

Interviewing participants who have consumed alcohol: Interviews should not proceed if an individual is intoxicated to the point of impaired capacity to consent. However, individuals who have consumed alcohol but retain the capacity to provide informed consent will be included in baseline and follow-up interviews.

Avoiding disruption to routine care: The researcher will ensure that the clinical team is fully aware of their whereabouts and those of the participants during the study. Should the participant be called to be seen by a clinician earlier than anticipated during the course of recruitment or data collection, the study survey measures will be suspended and resumed once the clinician has deemed it appropriate. Should the researcher become concerned for the participant's clinical condition, they will terminate the interview and immediately inform clinical staff of their concerns.

Information about results of study: Participants will be advised that results will be available on the University of Hull website and the website address will be contained within the PIS. Contact details for the study team are also included on the PIS in case participants wish to access the results in a different format.

7.5 Protocol Compliance

Protocol deviations

Accidental protocol deviations may occur at any time. Accidental protocol deviations will be documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Protocol Deviations which are found to frequently recur are not acceptable; these will require immediate action and could potentially be classified as a serious breach.

Investigators are required to promptly notify HHTU of a serious breach. A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for the conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the study participants, or the scientific value of the research.

Archiving

Electronic RCC database records and site files will be archived in accordance with the HHTU Archiving standard operating procedure and/or the NHS Trust archiving procedure after following submission of the end of study report and authorisation by the sponsor. All essential study documents held in the electronic site files will be archived for a minimum period of 10 years after study completion. Destruction of archived study documents will require authorisation from the sponsor.

7.6 End of Study

The end of the study will be after the NHS data for the admission, the 6-months prior to admission and the 6-months post admission have been provided by the NHS Trust (for consenting participants) and all data monitoring and quality control has been completed. NHS data will be requested after the last participant visit for the last participant at the research site.

7.7 Statement of Indemnity

This is an NIHR funded research study sponsored by the University of Hull and the Chief Investigator is primarily a University of Hull employee and will be covered by the University of Hull's standard clinical trials indemnity procedures. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff and medical academic staff with honorary contracts if the trial has received necessary governance approvals prior to recruitment. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

A statement of indemnity will be filed in the Trial Master File for HHTU and sponsor sites. Sites that include a member of staff with an honorary contract, will provide a copy of the honorary contract to HHTU.

7.8 Publication Policy

The data custodian will be the Chief Investigator. A publication policy will be developed and a core publication group will be appointed. The publication policy will contain guidelines on how to approach authorship and a regularly updated publication plan.

In line with current International Committee of Medical Journal Editors (ICMJE) guidelines, authorship credit should be based only on substantial contribution to:

- Conception or design of the work; or the acquisition, analysis or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contributors who do not meet all of the above criteria for authorship will not be listed as authors but will be acknowledged in any publication.

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