FULL PROTOCOL TITLE:

Prospective pragmatic quasi-experimental study to assess the impact and effectiveness of alcohol care teams (ACTs) targeting adults with alcohol dependence admitted to NHS Hospitals in England: the ProACTIVE prospective patient study protocol

SHORT STUDY TITLE:

The ProACTIVE Prospective Patient Study

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Chief Investigator(s):	Prof Thomas Phillips Professor of Nursing in Addictions Faculty of Health Sciences Institute for Clinical and Applied Health Research (ICAHR) Rm 325, Allam Medical Building University of Hull Hull HU6 7RX, UK thomas.phillips@hull.ac.uk 01482 464396 Prof Julia Sinclair Professor of Addiction Psychiatry Faculty of Medicine, University of Southampton julia.sinclair@soton.ac.uk
Sponsor:	University of Hull PVC-Research and Enterprise E-mail: pvc-re@hull.ac.uk
Funder:	NIHR Health and Social Care Delivery Research (HSDR) Programme (Ref: NIHR152084)
Trial statistician:	Professor Simon Coulton Centre for Health Services Studies, George Allen Wing University of Kent Canterbury CT2 7NF 01227 824535 S.Coulton@kent.ac.uk

PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Reason(s) for the protocol update
Current	1.0	21/Jul/2023	Prof Thomas Phillips	N/A

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...../...../.....

Print Name (in full): Thomas Phillips.....

Position: Professor of Nursing in Addictions.....

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LIST OF ABBREVIATIONS

ACT	Alcohol Care Team
ACTION	Alcohol Care Team Innovation and Optimisation Network
AMAU	Acute Medical Assessment Unit
APEASE	Acceptability, Practicability, Effectiveness, Affordability, Side-effects and Equity
AUDIT	Alcohol Use Disorders Identification Test
BFRS	Brief Family Relationship Scale
CICI	Context and Implementation of Complex Interventions
CIDI-alcohol	Composite International Diagnostic Interview-alcohol section
CNS	Central Nervous System
CSRI	Client Service Receipt Inventory
DARS	Data Access Request Service
DMEC	Data Monitoring and Ethics Committee
DSP Toolkit	Data Security and Protection Toolkit
ED	Emergency Department
EDC	Electronic Data Capture
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GHW	Gastro/Hepatology Wards
GMW	General Medical Wards
HES	Hospital Episode Statistics
HES-APC	Hospital Episode Statistics – Admitted Patient Care
HHTU	Hull Health Trials Unit
HISU	High-Impact Service User
HRG	Hospital Resource Group
ICB	Integrated Care Board
ICS	Integrated Care System
IMD	Index of Multiple Deprivation
ITS	Interrupted Time Series
LA	Local Authorities
LTP	Long Term Plan
MRC	Medical Research Council
NDTMS	National Drug (and alcohol) Treatment Monitoring System
NHS	National Health Service
NHSEI	NHS Improvement and NHS England
NIHR	National Institute for Health and Care Research
NN	Nearest Neighbour matching

NoACT	Minimal or No Alcohol Care Team
oACT	Optimal Alcohol Care Team
OHID	Office for Health Improvement and Disparities
ONS	Office for National Statistics
OSC	Oversight Steering Committee (for full ProACTIVE Programme)
PAG	Public Advisory Group
PHQ	Patient Health Questionnaire
PHE	Public Health England
PPI	Public and Patient Involvement
ProACTIVE	Programme of research for Alcohol Care Teams (ACTs): Implementation, Value and Effect
PSM	Propensity Score Matching
QALY	Quality Adjusted Life Year
RCC	RedCap Cloud
RCT	Randomised Controlled Trial
RGF	Research Governance Framework
SADQ	Severity of Alcohol Dependence Questionnaire
SMG	Study Management Group
SoECAT	Schedule of Events Cost Attribution Template
SOP	Standard Operating Procedure
TLFB	Timeline Follow Back
SWEMWBS	Short Warwick-Edinburgh Mental Wellbeing Scale
WP	Work Package

STUDY SUMMARY

Identifiers	
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Full (Scientific) title	Prospective pragmatic quasi-experimental study to assess the impact and effectiveness of alcohol care teams (ACTs) targeting adults with alcohol dependence admitted to NHS Hospitals in England: the ProACTIVE prospective patient study protocol
Health condition(s) or problem(s) studied	Alcohol dependence
Study Type i.e. Cohort etc	Quasi-experimental study
Target sample size	735
STUDY TIMELINES	
Study Duration/length	24 months
Expected Start Date	01/Oct/2023
End of Study definition and anticipated date	End of analysis and reporting: 30/Sept/2025
FUNDING	
Funding	NIHR Health and Social Care Delivery Research (HSDR) Programme (Ref: NIHR152084)
DATA MANAGEMENT	
Data Systems	Hull Health Trials Unit: Dr Judith Cohen, judith.cohen@hyms.ac.uk
KEY STUDY CONTACTS	
Chief Investigator	Prof Thomas Phillips, thomas.phillips@hull.ac.uk
Trial Manager	Dr Philippa Case, p.c.case@hull.ac.uk

1 Summary of research

Design: A pragmatic quasi-experimental study of three 'optimal' Alcohol Care Teams (oACTs; Intervention Group) and three 'minimal' or no ACT (NoACTs; Control Group) sites will recruit and follow up patients for six months to evaluate the impact of ACTs on patient and service outcomes. To draw causal inferences of the relative effect of oACTs, a counterfactual control group will be derived, using propensity score matching. Research procedures and materials have been developed in consultation with the ProACTIVE PPI collaborative.

Setting: NHS hospital sites in England. A national survey conducted by the ProACTIVE Research team in advance of this study will identify three hospital sites with fully established ('optimal') ACTs and three similar sites with minimal/no ACTs.

Population: Adults with alcohol dependence admitted to either the acute medical assessment unit (AMAU), general medical ward (GMW), or gastro/hepatology wards (GHW) who are willing and able to provide informed consent.

Inclusion criteria: Aged >=18 years, ICD-10 alcohol dependence and willing to be followed up by the research team at 6-months.

Exclusion criteria: Severe physical/mental illness identified by the treating clinicians, participation in another trial, unable to adequately understand verbal English, current dependence on an illicit substance.

Intervention sites - oACTs: Defined as hospital sites that host ACTs providing a service across the main hospital site offering consultation and liaison services ≥5days per week. The oACTs will demonstrate they generally operate within the service descriptors and specifications described by NHS England.

Control sites – NoACTs: Similar sized hospitals to the intervention sites with minimal or no ACT service provision. The hospital may operate to relevant clinical protocols but there is an absence of a comprehensive consultation or liaison service. A lone specialist practitioner or minimal in-reach teams (not daily) designed to receive referrals will meet the criteria of a minimal ACT.

Primary outcome measure: The primary outcome measure is alcohol consumption in the 28 days prior to the 6-month follow-up. Alcohol consumption is measured in units of alcohol, where one unit equates to 10ml (8g) ethanol using the Timeline Follow Back 28 (TLFB28).

Secondary outcome measures: TLFB28 will be used to derive percentage of days abstinent from alcohol, and quantity and frequency of other substances in the 28-day period prior to the 6-month assessment. Changes in the individuals experience of alcohol use and specific consequences will be assessed by Alcohol use Disorder Identification Test – (AUDIT), Severity of Alcohol Dependence Questionnaire (SADQ) and Alcohol Problems Questionnaire (APQ) as collected at baseline and at 6-month follow-up. Mental health and well-being will be measured using the Warwick-Edinburgh Mental Well-Being Scale (SWEMWBS) 7-item self-completed scale, the Personal Health Questionnaire to assess depressive symptoms (PHQ-9) and the Generalised Anxiety Disorder Assessment (GAD-7) at baseline, and at 6-month follow-up. Consent will be requested to access individual participant medical records to obtain the necessary information to calculate the Charlson Comorbidity Index (CCI) at baseline.

Economic outcome measures: NHS resource use, wider community resource use, and costs associated with wider community resource use will be assessed using the adapted Client Service Receipt Inventory (CSRI) and with the five domain and five level (EQ-SD-5L) generic health-related quality of life tool to calculate Quality-Adjusted Life Years (QALY) at baseline, and at 6-month follow-up.

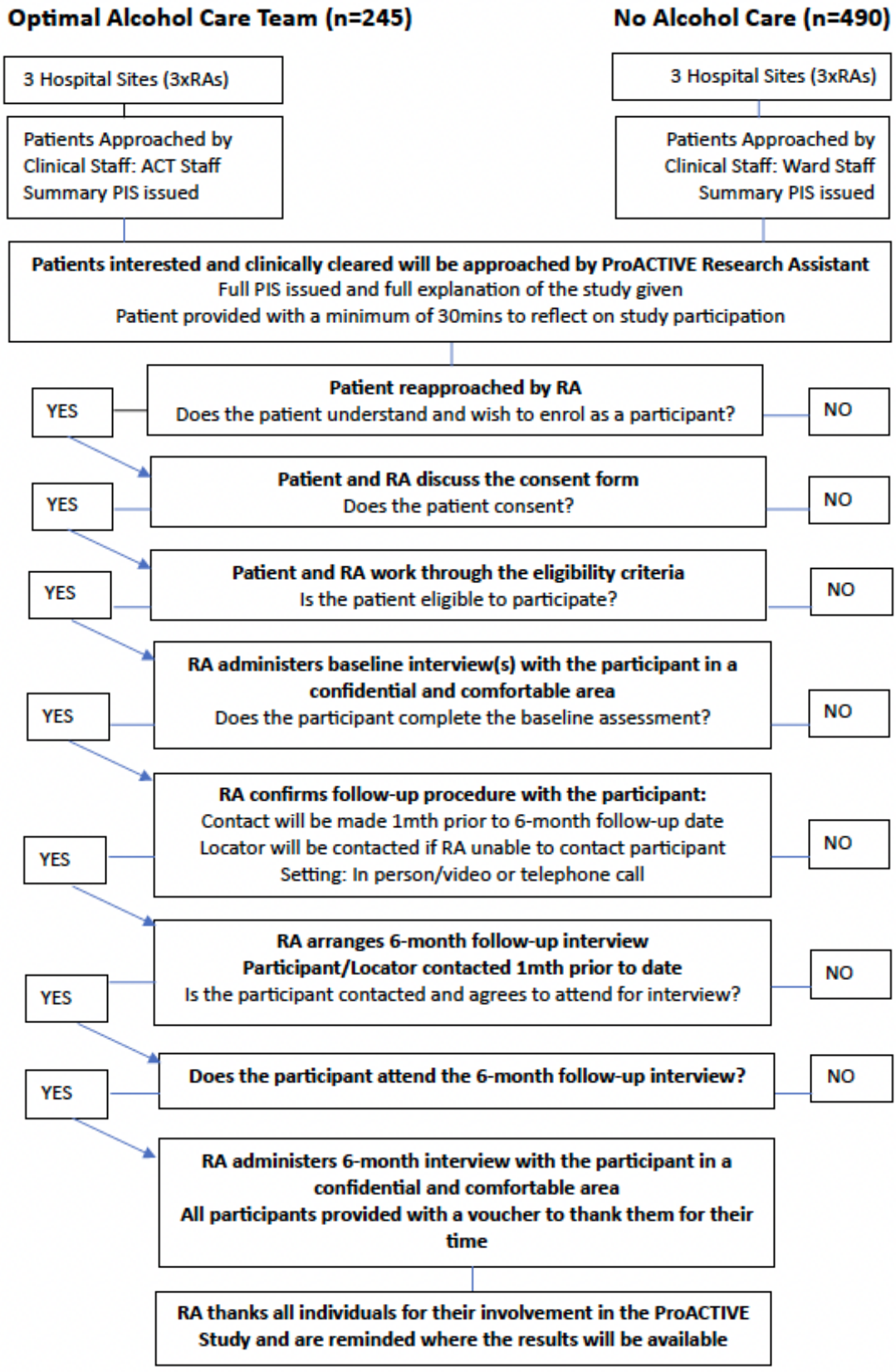
Primary analysis: The primary analysis will be analysis by treatment allocated (ATA), including all available data for participants. Alcohol consumed (AC) in the 28 days prior to the 6-month follow-up assessment will be analysed using analysis of covariance (ANCOVA) to compare the mean response across treatment groups, with fixed effects for treatment group, age, ethnicity and gender. The outcome will be adjusted for baseline alcohol consumption by including the baseline measure as a covariate. Results will be presented as mean differences between treatment and control groups, with accompanying 95% confidence intervals.

Economic analysis: Evaluation of oACT compared to hospitals with NoACT intervention on healthcare resource costs for people with alcohol dependence (AD) and an assessment of the short-term cost effectiveness of oACTs compared with control. We will combine individual resource use data with item-level cost estimates to estimate the total NHS and wider community costs for each individual in the 6-months prior to the baseline assessment and the 6-months between baseline and follow-up. This outcome will be analysed and presented in line with primary analysis, using analysis of covariance (ANCOVA) to compare the mean costs across treatment groups, with fixed effects for treatment group, age, ethnicity and gender.

Sample size: Three hundred and fifty potential participants will be approached in the intervention hospitals and 700 in the control hospitals. It is anticipated that approximately 70% of potential participants approached will consent, requiring a recruitment sample size of 735 participants. It is expected that 70% of those who consented will have complete 6-month follow-up data, meaning that baseline and 6-month data will be available for 175 participants in the intervention group and 350 participants in the control group (numbers rounded to include complete persons). Our recruitment estimates are sufficient to allow for estimation of at least a small, yet clinically important, standardized effect size difference in quantity of alcohol consumed between the groups of 0.3 with 90% power and a two-sided alpha of 0.05.

Propensity score matching (PSM): As the study is quasi-experimental, participants are not randomised. To draw causal inferences of the relative effect of oACT, a counterfactual control group will be derived, using PSM. A probit regression approach will be employed, blind to group source. Known covariates that are likely to be included in the model are: age, sex, quantity and frequency of alcohol use, severity of dependence and alcohol related problems, but these may be augmented with other variables if they emerge from the initial regression analysis. Callipers of width 0.2 of the standard deviation of the width of the logit propensity score will be employed to maximise matching. Once the propensity scores have been generated, they will be incorporated into the primary and secondary analysis using inverse propensity score weights.

1.1 Study Flow Chart



2 Study Management Group

This study will be managed by a Study Management Group (SMG) chaired by the Co-Chief Investigator (TP) and will include key co-investigators and the ProACTIVE PPI co-ordinator. Site and other collaborators will be included as required. The SMG will meet on a monthly basis throughout the course of the programme usually by teleconference.

2.1 ProACTIVE Oversight Steering Committee

The SMG will report to an independent ProACTIVE Oversight Steering Committee (OSC) chaired by Professor Sir Ian Gilmore which will be convened on a 6-month basis to approve the protocols and monitor the progress of the trial.

2.2 Data Monitoring and Ethics Committee

An independent Data Monitoring and Ethics Committee (DMEC), a sub-committee of the OSC, will convene on a 6-month basis to review study data and make recommendations to the OSC and SMG based on the ethical conduct and safety of the research.

2.3 ProACTIVE Programme Management Group

The SMG will additionally report to the ProACTIVE Programme Management Group. This group consists of all co-applicants on the ProACTIVE programme, plus the ProACTIVE Research Fellows and Research Assistants. The group meets every three months to review the progress of all work packages and advise on programme of research.

3 Background and rationale

3.1 Introduction

Following the launch of the NHS Long Term Plan (1), which aimed to increase multidisciplinary ACTs across the 25% of hospitals in England in greatest need, the Programme of Research for Alcohol Care Teams: Impact, Value and Effectiveness (ProACTIVE) Research Consortium was commissioned by the National Institute for Health Research (NIHR)[1] to bridge the evidence gap and evaluate the impact of ACTs in England using a mixed-methods approach.

In England, alcohol-related hospital admissions exceeded 1.26m in 2018/19, an increase of 155% over the preceding 15 years (2). Recent estimates identify 1 in 5 patients admitted to hospital drink at harmful levels, and 1 in 10 may be alcohol dependent (3). Chronic alcohol disorders including harmful drinking, alcohol dependence and alcohol-related liver disease have a disproportionate impact on the National Health Service (NHS) (4). Examination of routine hospital records in England (i.e. Hospital episode statistics – admitted patient care (HES-APC)) indicate a 30-day readmission rate of 19% (SD 5%) for those admitted to acute hospitals with an alcohol-related condition; with being of no fixed abode, experience of mental health problems, self-discharge and comorbid physical conditions being predictive of 30-day readmission (5). Prolonged and high-risk alcohol use is causally linked to over 60 medical diseases and conditions which commonly require inpatient care including cardiovascular disease, cancer and liver disease as well as harms caused by accidents and injuries (6). It is also recognised that mental health is negatively affected by prolonged and excessive alcohol use through an increased risk of common mental health problems, and impairments to memory and cognition. These disorders have been estimated to cost the NHS £3.5bn per year (7), with most of these costs related to emergency department (ED) attendances and hospital admissions.

Previous UK Government strategies have supported the development of hospital-based alcohol-care initiatives and services in response to rising admissions (8-11), resulting in the expansion of these services from 2008. The aim being that hospital-based alcohol provision will help reduce alcohol-related hospital admissions by increasing the quality of care and improved care pathways to community services (12). A 2013 survey of 191 acute hospitals in England identified 73% reported some level of specialist alcohol-care provision (13). These services fell into three broad models: 1) specialist hospital-based multi-disciplinary teams (known as Alcohol Care Teams (ACTs)); 2) specialist in-reach team/worker provided by community addiction services; and 3) community based high impact service-user (HISU) teams (e.g. alcohol assertive outreach teams). The survey identified 30 (15.7%) hospitals that had developed a multidisciplinary ACT but found significant variation in size, scope and level of interventions, and clinical leadership provided across these teams.

Although there is clinical consensus that multidisciplinary ACTs are needed to address the rising impact of alcohol-related harm and emergency admissions to acute hospitals (14, 15), there is a lack of evidence as to the clinical and cost-effectiveness of these services in reducing alcohol-related hospital admissions in England. Previous studies have examined the impact of alcohol specific interventions such as screening and brief intervention (16-18), medically assisted alcohol withdrawal (19, 20) and relapse prevention medication (21, 22) in acute hospitals but there is surprisingly limited published literature evaluating the impact of ACTs in reducing alcohol-related hospital admissions within the

[1] https://fundingawards.nihr.ac.uk/award/NIHR152084

NHS in England. The evidence supporting the expansion of ACTs under the NHS Long Term Plan (1) relies on a previous quality improvement report (23) that highlighted the possible gains in reducing alcohol-related hospital admissions and hospital lengths of stay. The report highlights single site clinical audits (24) and service evaluations (25) and estimates a 7-day hospital-based alcohol nurse service would provide a net saving, in occupied bed days, of approximately £448,000 per annum based on a hospital population of 250,000.

In 2018, prior to the launch of the NHS Long Term Plan (1) it was estimated the number of multidisciplinary ACTs providing a range of interventions (i.e. screening, brief interventions, comprehensive assessment, medically managed alcohol withdrawal, etc), had risen to 60, with variations in scope based on size of hospital, local need and available funding. A number of these multidisciplinary ACTs demonstrated 'optimal' services operating 7-days per week, offering a full range of patient level interventions, as well as staff training and collaborative care with community providers. The NHS Long Term Plan (1) committed to spend £26m over four years (until mid-2024) to 'optimise' ACTs through the development of existing services and the establishment of new teams in the 25% of hospitals in greatest need in England. In this context 'optimisation' involves funding to offer a 7-day service to deliver a range of patient and system level interventions to improve the identification and management of alcohol dependent patients. A range of service models have evolved, supported by existing clinical guidelines, to assess and treat individuals with alcohol use disorders. Comparisons between optimal ACTs (oACT) and those with minimal or no ACT (NoACT), allows for evaluation of the most effective and cost-effective components and models of ACTs.

3.2 Background

The development of ACTs was driven primarily from a narrow service-use model of the short-term management of alcohol dependence within an acute setting (19) based on individual hospital case-studies, and there has been no robust national evaluation of the impact of implementing ACTs more broadly.

A recent systematic review has examined the international literature related to hospital-based addiction/alcohol service models to consider the impact of interventions on the transitions in care between acute hospital care and community settings for individuals with a substance use disorder (26). Overall, 31 published articles met the inclusion criteria with nine studies using a range of methodological approaches to examine the impact of services for those hospitalised with alcohol use disorders.

Randomised Controlled Trial

Schwarz et al (27) conducted a pragmatic RCT within an acute hospital setting in Denmark, examining differences in the uptake of specialist community alcohol treatment at 18 months by those with AUD receiving screening brief intervention and referral to treatment plus a consultation service (Relay) (i.e. intervention) compared to treatment as usual (i.e. control) during their hospital admission. The results identified overall specialist treatment uptake was low, and whilst the intervention was found to significantly increase the odds of post discharge treatment engagement in those scoring AUDIT 8-15, there was no significant difference between the intervention or control groups in those with harmful or dependent drinking (i.e. AUDIT 16+ score).

Quasi Experimental Studies

Schwan et al (28) examined the impact of repeated brief interventions delivered by an alcohol liaison team (i.e. the intervention) to a total of 203 patients admitted to an acute medical ward with alcohol problems. This longitudinal control study compared readmission rates among patients previously admitted to ED for the same reason and found those receiving the intervention experienced a decrease of 45% in readmission rates compared to control (standard care) at 12 months. A quasi-naturalistic prospective follow-up study compared attendance at post-alcohol treatment visits in 60 unscheduled alcohol withdrawal admissions from ED versus 60 planned admissions for alcohol withdrawal in France and found no significant differences in dropout rates or post-discharge addiction treatment attendance (29).

Wakeman et al (30) conducted a non-randomised prospective quasi-experimental evaluation in one hospital in the US investigating the impact of an addiction consultation service among 399 admitted individuals with alcohol or drug use disorder with 256 receiving the intervention having been admitted to wards with the consult service and controls (n=143) being admitted to wards without the consultation services. Outcomes considered changes in Addiction Severity Index (ASI) composite scores for drug and alcohol use, self-reported abstinence at 30-days post discharge and self-reported hospital utilisation and found those receiving the intervention had significantly greater reductions in ASI composite scores (mean ASI-alcohol decreased by 0.24 vs. 0.08, $p < 0.001$; mean ASI-drug decreased by 0.05 vs. 0.02, $p = 0.003$), and greater increases in the number of self-reported abstinence days (+12.7 days vs. +5.6, $p < 0.001$) than controls, which remained statistically significant after controlling for confounders. Secondary outcomes identified significant reductions for hospital readmissions (61 % vs. 51%, $p < .01$), ED attendances (66 % vs. 53%, $p < .01$) and significantly higher likelihood of engaging in addiction treatment post-discharge (n = 399, 58 % vs. 41 %, $p = .009$ % at 30 days and 55 % vs. 41 %, $p = .05$ at 90 days) amongst those receiving the intervention compared to controls.

Cohort study employing propensity score matching

Englander et al (31) used propensity score matching to compare participants in receipt of medical addiction consult services (intervention; 208 participants with non-opioid (including individuals with alcohol and stimulants) or opioids disorders) with usual care and found those receiving the intervention had a greater odds of accessing post-discharge treatment (AOR 2.15, 95%CI 1.29-3.58, p<.01), however, a sensitivity analysis identified those with opioid disorder were more likely than those with non-opioid disorders to engage in treatment (AOR 1.83, 95%CI 1.03-3.24).

Case control study employing propensity score matching

Wilson et al (32) conducted a propensity-score-matched case-control study in a single hospital site investigating patients presenting with substance misuse seen by the hospital consultation service (n=711) from 2018 to 2020 who were matched to those previous admitted and not seen by the consultation service (n= 2,172) from 2017 to 2018. Outcomes considered 90-day post-discharge mortality, ED reattendance and hospital readmission, with a sub-analysis of participants with alcohol use only. Overall, the intervention group experienced significant reductions in 90-day mortality (average treatment effect [ATE]: −2.35%, 95% CI: −3.57, −1.13; p-value <0.001) and 7-day hospital readmissions by 2.15% (95% CI: −3.65, −0.65; p=0.005) and a non-significant reduction in 30-day

readmission (ATE: −2.38%, 95% CI: −5.20, 0.45; p=0.099), but a significant increase in 30-day ED visits (ATE: 5.32%, 95% CI: 2.19, 8.46; 0.001) compared to controls. For those exclusively with an alcohol use disorder, the intervention group (n=181) experienced only a significant reduction in 90-day post-discharge mortality [ATE]: −4.08%, 95% CI: −6.12, −2.04; p-value <0.001) compared to controls (n=684).

Programme Evaluations

Trowbridge et al (33) provided a programme description of a specialist addiction consultation service in one hospital in the US and reported on the proportion of participants who received specialist medications and subsequently engaged in community treatment 0-, 30-, 90- and 180-days post discharge. Only 12% of those with an AUD (n=125) received naltrexone to support relapse prevention in alcohol dependence with engagement rates amongst those receiving naltrexone being 33%, 27%, 13% and 0%, respectively. Wei et al (34) evaluated the introduction of an inpatient treatment and planning protocol for the care of patients admitted with alcohol use disorders comparing outcomes for all cause 30-day readmission and ED attendance rates before and after implementation of the protocol (June 2011 versus March 2012) in one hospital in the US. The reported outcomes include significant reductions in 30-day readmissions and non-significant reductions in 30-day ED reattendances, however, the study makes comparisons at two different time points, and the lack of randomisation does not allow causality to be proven.

Pre- and Post- Studies

Deng et al (35) conducted a feasibility study of 843 participants and examined the impact of transitioning from an in-person consultation (pre-pandemic period) and liaison service to a telehealth intervention (provided during the pandemic) through reductions in 30-day hospital readmission rate which included 45% of participants with an AUD. The study reports decrease in 30-day readmissions in the telehealth group, but no statistical analysis was conducted and no specific observations regarding those with AUD were made. A pre-post study examined the impact of specialist counselling and naltrexone on 30-day readmissions and ED attendances among individuals admitted to an acute hospital in the US for alcohol withdrawal management and found the introduction of the intervention significantly lowered 30-day ED attendances but not readmissions (36).

3.2.1 Summary

The existing evidence for hospital-based interventions for people with alcohol use disorders shows some promise in reduced readmission rates and fewer ED attendances, although some of the study designs in the existing literature do not make it possible to unequivocally attribute causality to the interventions. The vast majority of studies are drawn from North America with only two studies being conducted in Europe (Denmark and France) and without exception all studies included only one hospital site. Therefore, despite the increasing trajectory of alcohol-related hospital admissions and broad consensus for the need for alcohol care teams in England there remains a paucity of evidence regarding their effectiveness and impact nationally, or internationally using similar service models. Our programme of research will therefore be the first UK and first multi-centre study to examine the impact, value and effectiveness of hospital-based alcohol care.

4 Aims and objectives

4.1 Aim:

1. To evaluate the effectiveness of hospitals with an established oACT compared to hospitals with NoACT intervention for people with alcohol dependence (AD) based on the quantity of alcohol consumed six months after admission.

4.2 Objectives:

I. To conduct a quasi-experimental study to assess the effectiveness of oACT compared to NoACT in improving outcomes for adults admitted to hospital in England with alcohol dependence.

II. To estimate the cost effectiveness of oACT compared to NoACT in enhancing quality adjusted life years and impact on NHS and wider community resource use.

III. To conduct an exploratory analysis to identify the factors that predict changes in outcomes at 6-months.

Primary hypothesis:

i. oACT will be no more effective than NoACT in terms of self-reported alcohol consumption, measured using Timeline Follow Back 28 at 6 months.

Secondary hypothesis:

i. oACT will be no more cost-effective than NoACT at 6-months.

5 Study Design

The aim of this study is to provide estimates of the effect of an oACT on individual participant outcomes. In this study a randomised design is not feasible or practical for several reasons. First, ACTs already exist in a variety of forms so we cannot have any true control sites with no prior exposure to, or any knowledge of, ACTs. Second, those ACTs that already exist have taken a great deal of time to mature and be embedded within the health care system. While we gave significant thought to the possibility of conducting a form of RCT, possibly a stepped wedge RCT, we feel that time, costs and a desire to produce pragmatic and generalisable findings requires an alternative methodological approach. A well designed quasi-experimental approach can provide evidence of the relative effectiveness of an intervention when compared with a control, and Medical Research Council (MRC) Complex Interventions guidance acknowledge that designs other than RCTs are considered appropriate for 'natural experiments' when interventions are being implemented already (37), as is the case with ACTs. The key issue is that the lack of randomisation may mean the baseline characteristics of the groups are not comparable and any effects estimated may potentially be biased. In order to address this potential bias we propose to generate an equivalent control group using a propensity score matching approach (38).

The propensity score, derived from baseline covariates in the intervention groups using a logistic regression approach, is a balancing score. Hence, in a set of subjects who all have the same propensity score, the overall distribution of baseline covariates will be the same between intervention and control groups. This allows a non-randomised study to mimic the characteristics of a randomised study with both intervention and control groups.

6 Method

6.1 Target population and sample

The target population for this study is adults with alcohol dependence admitted to participating hospitals. The majority of individuals with alcohol dependence are admitted to acute medical assessment units (AMAU), general medical wards (GMW), or gastro/hepatology wards (GHW); however, all wards of each hospital will be considered eligible.

6.1.1 Inclusion and exclusion criteria

Inclusion and exclusion criteria have been selected so that the sample population will be broadly representative of those targeted by ACTs in normal practice.

6.1.1.1 Inclusion criteria

i. Adult aged >= 18 years.
ii. An ICD-10 diagnosis alcohol dependence as measured by Composite International Diagnostic Interview (CIDI)-alcohol.
iii. Patient admitted to a participating hospital.
iv. Agrees to be contacted by the research team and participate in a follow-up data collection at 6-months.
v. Judged by clinical staff to be medically and psychologically fit enough to participate in the study.
vi. Willing and able to provide informed consent to take part in the trial.

6.1.1.2 Exclusion criteria

i. Severe physical/mental illness likely to preclude active participation in baseline or follow-up data collection.
ii. Current participation in another research study.
iii. Unable to adequately understand verbal English due the majority of the validated measures being available in English only.
iv. Currently prescribed opioid substitution therapy.

The characteristics and reasons for exclusion for excluded patients will be captured to identify any specific groups who may be under-represented in this study.

6.1.2 Setting and context

Participants will be recruited from one of six acute hospitals in England, each will have an assigned ProACTIVE researcher to recruit study participants. Whilst the national adult community prevalence for alcohol dependence is estimated at 1.35% (95%CI 1.11-1.71) there is considerable range across local authorities from 0.65% (95%CI 0.43-1.03) to 3.91% (95%CI 1.51-9.51) (39). There is a significant positive correlation between community prevalence of alcohol dependence and hospital admissions, with hospital-based prevalence being magnified due the causal relationship between excessive and prolonged alcohol use and multiple co-morbid diseases and conditions (40). A recent meta-analysis conducted by a member of our research team has identified that 10.25% (95% CI = 7.06–13.96%) of hospital admissions are estimated to involve people with alcohol dependence, though not all of these admissions are for alcohol-related causes (3). The evidence from administrative data and clinical

activity identifies most individuals with alcohol dependence are admitted to acute medical assessment units (AMAUs), general medical wards (GMW) and gastro/hepatology wards (GHW) (5) and we will therefore start recruitment in these wards. We are confident that there will be a large pool of eligible patients who can be approached at each participating hospital.

6.1.2.1 Intervention sites – Optimal Alcohol Care Teams (oACTs):

Our intervention sites will include three hospitals identified as having an oACT, which are defined as hospital sites that host ACTs that offer a full range of patient level interventions, operate 7-days per week, and deliver staff training and collaborative care with community providers. Analysis of hospital-based services in England conducted by Public Health England in 2018 identified that 140/190 acute hospital hosted hospital-based alcohol teams with between 28-48 ACTs meeting the criteria for oACT. In order to maximise generalisability, we aim to recruit oACTs from areas of high alcohol dependence prevalence (i.e. North of England), lower alcohol dependence prevalence (i.e. South of England) and an urban conurbation with a diverse ethnic population (e.g. Midlands). In oACT hospitals all alcohol dependent patients seen by the ACT over the recruitment period will be assessed and invited to participate.

6.1.2.2 Control sites – No or minimal Alcohol Care Team (NoACTs):

Our control group will consist of three hospitals matched for hospital size and population demographics with minimal or no ACT service provision. The hospital may operate to relevant clinical protocols but there is an absence of a comprehensive consultation or liaison service. A lone specialist practitioner or minimal in-reach teams designed to receive referrals will meet the criteria of a minimal ACT. In the non-ACT hospitals, we will implement a recruitment strategy that emulates the inclusion criteria for ACT intervention and approach patients who would have been seen by an ACT if one existed.

6.1.3 Sample Size

Over the six-month recruitment window, we conservatively estimate at least 250 potential participants will be admitted to each of the six hospitals, and we aim to identify and approach 350 across the intervention hospitals and 700 across the controls, of whom we anticipate 70% will consent leading to a target recruitment sample of 735 participants (N=245 in oACT sites and N=490 in NoACT sites) (41). We would expect 70% of these will be followed up at month 6 (41, 42), 175 in the oACT group and 350 available for matching in the control group, from which a control sample of 175 will be matched.

Our recruitment estimates are sufficient to allow for estimation of at least a small, yet clinically important, standardized effect size difference in quantity of alcohol consumed between the groups of 0.3 with 90% power and a two-sided alpha of 0.05.

6.1.3.1 Levels of confidence and p-values

Unless otherwise specified, estimates will be presented with 95% confidence intervals. Significance tests will be two-tailed, and a significance level of <0.05 will be considered statistically significant. This study has a predefined primary outcome measure, at a specific time point and involves a single comparison between two treatment groups, therefore no adjustment for multiplicity is required.

Secondary outcomes generated from the TLFB will be presented as descriptive statistics with no formal analysis.

6.1.3.2 Evidence to support the feasibility of achieving the required sample size

A number of trials conducted amongst individuals with alcohol dependence have been conducted in the UK, most have included researchers who are part of the ProACTIVE team. They have all demonstrated feasibility of recruiting and following-up individuals with lived experience of alcohol dependence. The United Kingdom Alcohol Treatment Trial (43, 44) was a pragmatic randomised trial that planned to recruit 720 individuals attending specialist alcohol treatment to test the effectiveness and cost-effectiveness of Motivational Enhancement Therapy and Social Network Behavioural Therapy employing a follow-up strategy at 3- and 12-months. This study recruited 742 participants and obtained a 93% follow-up rate at 3-months and 83% at 12-months. Similarly, a pilot randomized controlled trial (RCT) to assess the feasibility and potential efficacy of assertive community treatment (ACT) in adults with alcohol dependence (41) recruited a total of 94 high need participants who were randomized, 45 to ACT and 49 to treatment as usual. Follow-up was achieved with 98% at 6-months and 88% at 12 months.

A recent complex medicine adherence randomised controlled trial (ADAM Study – National Institute for Health and Care Research (NIHR) Award 13/86/03) to determine the efficacy of medication management with and without contingency management in comparison to treatment as usual in patients with alcohol dependence achieved the recruitment target of 748 participants and the 6-month follow-up rate of 70%. The research site which recruited participants from the ACT within an acute hospital achieved > 80% follow-up rates at 6-months. Finally, an observational follow-up study of 141 patients with alcohol dependence admitted to an acute Trust (45) obtained a follow-up rate of 94% at six months.

Together these studies demonstrate the feasibility of conducting research trials amongst this population who appear to value the opportunity to engage. Our experience has taught us that well designed and clear recruitment strategies describing follow-up procedures are essential. These involve the use of personal ‘locaters’, who are individuals nominated by the participants from within their circle of concern who can assist the research team in locating the participant should they be unable to respond to a follow-up request (e.g. due to hospital admission, loss of accommodation, prison etc). However, our experience and analysis of routine administrative data also suggests that the stereotype that people with alcohol dependence seen in acute hospitals are more likely to be in transient populations is incorrect. Recent analysis of national hospital datasets for alcohol withdrawal admissions identifies only 2.7% of these individuals are recorded as being of no fixed abode (5).

6.2 Participant Recruitment

All patients who meet the inclusion criteria will be identified by the alcohol care team (oACT sites) or by the clinical teams on participating hospitals wards, starting with AMAU, GMW, and GHW (NoACT sites).

6.2.1 Initial approach

Potential participants will be initially contacted by a member of the ACT or clinical team to ask if they would be willing to speak with a member of the ProACTIVE research team about the study. The clinical team will make a judgement as to the patient’s ability to participate in the study and, where

appropriate, a member of the clinical team will describe the study, provide the summary document, and obtain verbal agreement from the patient for the researcher to approach them to discuss the study further. A member of either the clinical or research team will provide the patient with the participant information sheet (PIS) and the researcher will subsequently contact the patient to provide additional details of the nature and purpose of the research and answer any questions the patient may have.

6.2.2 Informed consent and initial assessment

The average admission for a patient experiencing alcohol dependence is three days. The recruitment process requires the researcher to work closely with the clinical team to identify and approach potential participants. A consent and initial assessment appointment will then be made. 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. In a draft version of this protocol, a 24hr period was suggested, but the ProACTIVE PPI representation suggested removing or reducing the time limit, indicating that some people would wish to consent and participate on the same day. A similar project has been conducted in emergency medicine in the UK (IRAS 275280) which allowed a minimum of 30 minutes between ED attenders receiving the PIS and providing consent.

With the agreement of the clinical team and the patient, a confidential area will be identified where the research interview (collection of research data using quantitative questionnaires) can be conducted. The clinical team will be made aware that the patient will be participating in a research interview should they need to be contacted for any clinical reason (i.e. medical review, medication round, etc). It will be made clear that clinical care should not be impeded due to participation in the research project and the research interview will be suspended should the participant need to access any form of care. The clinical team will be notified once the research interview has been completed.

During this appointment, the researcher will go through the PIS with potential participants, clearly explaining the aims of the study and what it will involve. This discussion will include the optional consent to access their medical records for their current admission, their optional consent to nominate a locator to support follow-up interviews at 6-months and their optional consent to be contacted about participation in a qualitative interview. The optional qualitative interview is part of a qualitative research study that will run alongside this study with a linked IRAS application, and separate consent will be obtained for the qualitative interviews. Access to the participant's medical record pertaining to their current admission is requested to ascertain the length of this admission and identify primary and secondary diagnoses which are needed to characterise the clinical complexity of the patients in the analysis. A named locator is requested to support contact with the participant at 6-months. This individual is typically a family member, carer or significant individual who is happy to assist the research team in contacting the participant at 6-month follow-up. The participant will be provided with a brief information sheet (found at the back of the PIS) informing the locator of the nature and purpose of the information held by the research team. This information will include details of how to opt out of having their information held.

Informed consent to take part will be collected electronically by a trained researcher at this initial assessment, the voluntary nature of the research will be highlighted including the right to withdraw

at any time. The participant should only sign the electronic consent (e-consent) form after a discussion to confirm understanding of the research study, including their full understanding of the nature, significance, implications and risks of the study. No research activities will take place prior to the signing of the e-consent form. A copy of the consent will be sent to the participant via email or to a postal address if they don't have an email address.

For patients giving consent to participate, all inclusion criteria will be reviewed and a diagnosis of alcohol dependence according to ICD-10 criteria will be confirmed using the CIDI-alcohol (46). Exclusion criteria will be assessed through interview with the participant to ensure that the patient is suitable to take part in the study.

6.2.3 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 of 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. Data collected up to the time of withdrawal will be used in analysis. Withdrawn participants will be replaced as far as possible within the constraints of the study timelines.

6.3 Data collection

6.3.1 Baseline data collection procedure

Baseline data collection can either take place immediately following the consent and initial assessment interview or can be arranged for a later time if requested by the patient or clinical team. At baseline, a member of the research team embedded at participating sites will collect data from consenting participants during a face-to-face assessment in a confidential area of the hospital in which the participant is an inpatient. Researchers will make it clear to participants that they are not part of the clinical team, that no information they provide will be shared with the clinical team (within the boundaries of confidentiality), that there are no right or wrong answers and that they are blind to assessment results. It is anticipated that the baseline interview will take approximately 60 minutes and participants will be given the opportunity to take breaks if needed.

Data will be collected relating to demographic characteristics (age, sex, ethnicity, living situation), family environment assessed using the Brief Family Relationship Scale (BFRS; (47)), and socio-economic status derived from the Index of Multiple Deprivation (IMD) associated with patient postcode). Demographic information will be used for characterising the sample and propensity score matching, as these factors could influence the study outcome measures. Alcohol consumption (age of first drink, age of daily drinking, quantity and frequency of alcohol consumed over the 28 days prior to hospital admission assessed using standard Timeline Follow Back methods (TLFB; (48)) and Alcohol Use Disorders Identification Test (AUDIT (49)) alcohol dependence (measured using the Severity of Alcohol Dependence Questionnaire (SADQ; (50)) and the Alcohol Problems Questionnaire (APQ; (51)) will all be collected. Quantity of alcohol consumed in the past 28 days at month 6 is the primary outcome measure, and this is derived using the TLFB. The additional alcohol questions are secondary outcome measures that will be used to establish severity of alcohol problems in the sample, to identify any changes at follow-up and may be used for propensity score matching. In recognition of the complex needs of people accessing hospitals for alcohol-related conditions, data on a number of key comorbidities will also be collected: quality of life (assessed using the 5-level EuroQol EQ-5D (EQ-5D-

5L; (52)); wellbeing (assessed using the 7-item Warwick-Edinburgh Mental Wellbeing Scale (SWEBWMS; (53)); common mental disorders (assessed using the Patient Health Questionnaire (PHQ-9 (54)) and the Generalised Anxiety Disorder scale (GAD-7; (55)); co-occurring drug use (assessed using the 28 day TLFB method) and, for patients who consent to their medical records being accessed, the Charlson Comorbidity Index (56).

Service use over the previous six-months including alcohol specific treatment and support services will be collected using the Client Service Receipt Inventory (CSRI) specifically designed for this population, the questionnaire covers all forms of health and social care and includes contacts with the police and criminal justice services (41).

At the end of the baseline interview, all participants will be reminded about the follow-up interview and will be informed that they will be contacted up to four weeks before their follow-up interview is due to arrange a time. Participants will be prompted to inform their identified locator (if applicable) that their contact details have been given to the research team and to explain that they might be contacted. They will be encouraged to provide the locator with the information at the back of the PIS. Participants will also be reminded that they will receive a £10 thank you voucher for taking part in the research at the end of their follow-up interview.

With the exception of demographic information, the BFRS and the CIDI, all measures will be repeated at 6-month follow-up by a researcher. The outcome battery has been used in several studies with a similar population. All the outcomes demonstrate excellent psychometric properties in this population and take approximately 60 minutes to complete. Table 1 outlines the study outcome measures and timing of their administration during the study.

Table 1: Study outcome measures

	Baseline	6-month Follow Up
CIDI - alcohol	x	-
Demographics (age, sex, ethnicity, living situation)	x	-
Socio-economic status	x	-
Patient postcode	x	-
Age of first drink and daily drinking	x	-
Timeline Follow Back 28 (alcohol)	x	x
Timeline Follow Back 28 (drug use)	x	x
AUDIT	x	x
APQ	x	x
SADQ	x	x
SWEBWMS	x	x
PHQ-9	x	x
GAD-7	x	x

Brief Family Relationship Scale (BFRS)	x	
EQ-5D-5L	x	x
CSRI	x	x
Optional consent to access medical records for admission information (primary and secondary diagnosis) to allow for calculation of Charlson Comorbidity Index and to obtain discharge code.	x	-

Research and personal data will be collected via an electronic data capture tool specifically designed for this research study by the Hull Health Trials Unit (HHTU) using the commercially available system REDCap Cloud (RCC). Laptop computers or tablets will be used for data collection. All electronic devices used for the study will be password protected. Data will be entered and saved directly into RCC, with data residing on a secure server with a 256bit encryption, no data will be saved directly onto the laptop computer. Research data will be anonymised by assigning each participant a unique ID number, personal data will be stored separately to the research data to maintain participant anonymity.

6.3.2 Follow-Up Data Collection Procedure

Follow-up procedures from an NIHR-funded 3-arm randomised controlled trial (ADAM study [2]) will be adapted for this study. Members of the research team will commence contact with participants for their follow-up appointments one month before their follow-up appointment is due and will allow two months from the commencement of contact to book and conduct the follow-up interview. Frequent attempts to contact the participant or their locator will be made during this time. Appointments will be confirmed via text or email one day prior to the interview date.

Participants will have the option to complete the follow-up interview over the telephone, via a video call, or face-to-face depending on their preference. Participants may no longer be under the care of the clinical sites at the time of follow-up, meaning that there may be no means of conducting a risk assessment prior to the follow-up interview. Therefore, face-to-face follow-up interviews will be conducted in either agreed clinical settings, such as a room in an outpatient clinic of the participating site, or in quiet areas of public places, such as cafes, community centres or parks. All follow-up interviews will adhere to the University of Hull lone working procedure.

Both during the initial contact with participants to arrange the follow-up appointment, and during the appointment itself, researchers will proactively ascertain whether the individual still wishes to take part and whether the individual retains the capacity to give informed consent.

At the end of the interview, all participants will be thanked for their time and contribution and will be given a £10 shopping voucher.

6.3.3 Primary outcome measure

The primary outcome measure is alcohol consumed in the 28 days prior to the 6-month follow-up. The primary outcome is derived using Timeline Follow Back 28 (TLFB28 (48)) which measures the quantity

[2] https://fundingawards.nihr.ac.uk/award/13/86/03

and frequency of substance use over 28 days. Alcohol consumption is measured in units of alcohol, where 10ml/8g ethanol = 1UK unit of alcohol. TLFB is a valid and reliable tool for assessing the quantity and frequency of substance use over time periods ranging from 1 to 365 days. The outcome has been validated and recent pilot work has indicated high levels of agreement between the shorter, 28-day, and longer 90-day, reference period. In addition to alcohol consumption the tool allows derivation of a number of secondary outcomes described in the section below. TLFB28 is completed by a trained member of research staff and takes approximately 20 minutes.

6.3.4 Secondary outcome measures

TLFB28 secondary outcomes

A number of secondary outcomes will be derived from TLFB28. These outcomes are the percent days abstinent for each of the 11 recorded types of substance (alcohol, cannabinoids/marijuana, cocaine, crack, amphetamine-type stimulants, opioid analgesics (including methadone), heroin, hallucinogens (including MDMA/ecstasy), sedatives and hypnotics (excluding benzodiazepine), benzodiazepines and inhalants) and the quantity of each substance used in the 28-day period prior to the 6-month assessment. The TLFB28 will be completed at baseline and at 6 month follow-up.

Alcohol Use Disorder Identification Test (AUDIT (49):

AUDIT (Alcohol use Disorder Identification Test) 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.

Alcohol Problems Questionnaire (APQ (51)):

Alcohol related problems will be assessed at initial screening assessment and then at 6-month follow-up, using the Alcohol Problems Questionnaire (APQ). 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.

Severity of Alcohol Dependence Questionnaire (SADQ (50)):

Severity of dependence will be measured at the initial screening assessment and at 6-month follow-up using the Severity of Alcohol Dependence Questionnaire (SADQ). 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.

Warwick-Edinburgh Mental Well-Being Scale (SWEMWBS (53)):

Mental health and well-being will be measured using the short Warwick-Edinburgh Mental Well-Being Scale (SWEMWBS) at baseline, and at 6 months follow-up. SWEMWBS is a self-completed scale addressing different aspects of eudemonic and hedonic mental health wellbeing. The WEMWBS has both a 14-item and a 7-item (SWEMWBS) version and the 7-item version will be used in this study to minimise participant burden. The scale has established validity and reliability and established sensitivity to change.

The SWEMWBS total score will be derived by summing the individual items score. Where more than 3 individual item scores are missing the total score will be assumed to be missing. Where 3 or fewer items are missing the total score will be estimated using mean substitution for missing values. Individual items scores will be checked for systematic missingness by comparing the proportion of missing values by age, gender, hospital and treatment group.

Patient Health Questionnaire (PHQ-9 (54))

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 (57). 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 mild (5-9), moderate (10-14), moderately severe (15-19) and severe (20-27) depressive symptoms.

Generalised Anxiety Disorder scale (GAD-7 (55))

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 of 5, 10, and 15 are taken as the cut-off points for mild, moderate and severe anxiety, respectively. Additionally, the GAD-7 is able to screen for panic disorder, social anxiety disorder and post-traumatic stress disorder.

EQ-5D - five domain and five level (EQ-SD-5L, (52))

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.

Client Service Receipt Inventory (CSRI):

NHS and community resource use data will be collected alongside WP2a data collection using a Client Service Receipt Inventory (CSRI) in which individuals will be asked to report their service use across a range of health and care services over the past 6 months. This study will use a version of the tool used in previous alcohol research (41) which starts with a section that is specific to treatment for drinking problems (i.e. contacts and venues for counselling, day care, detoxification, outpatient treatment; details of overnight stays and interventions and details of medication – all specific to alcohol treatment). These data will be collected at both baseline and 6-month follow-up. Item-level costs for each item will be obtained from the most recent published Personal Social Services Research Unit (PSSRU) unit costs or other published estimates where appropriate.

Charlson Comorbidity Index (CCI (56)):

Consent will be sought to access individual participant medical records and obtain the necessary information to calculate the Charlson comorbidity index. The index takes account of 19 pre-defined co-morbid conditions and provides a weighted score of an individual's comorbidities which can be used to predict short term and long-term health outcomes.

7 Data analysis

7.1 Propensity score matching

As the study is quasi-experimental, participants are not randomised. To draw causal inferences of the relative effect of oACT, a counterfactual control group will be derived, using propensity score matching (38). A probit regression approach will be employed, blind to group source. Known covariates that are likely to be included in the model are: age, sex, quantity and frequency of alcohol use, severity of dependence and alcohol related problems, but these may be augmented with other variables if they emerge from the initial regression analysis. Callipers of width 0.2 of the standard deviation of the width of the logit propensity score will be employed to maximise matching (58, 59).

Once the propensity scores have been generated, they will be incorporated into the primary and secondary analysis using inverse propensity score weights.

7.2 As Treatment Allocated (ATA)

The primary analysis will be based on the analysis by treatment allocated (ATA) dataset, which contains all available data for participants who were recruited regardless of whether or not they complied with allocation. This dataset will include participants who were withdrawn/withdrew from the study. These analyses are a lower bound estimate of treatment effects as they represent the effect of offering a programme, rather than the effect of actually receiving that programme.

7.3 Per protocol dataset (PP)

Contains all data for all eligible participants who were recruited from one of the participating sites, remained in hospital until discharged and did not discharge against medical advice, and have complete data at baseline and 6 months. Participants will be analysed in the group to which they were recruited, oACT or NoACT. The Per Protocol dataset represents a likely ‘best case scenario’ for treatment effect estimation.

7.4 Missing data

The proportion of missing data and patterns of missingness will be examined for the primary and secondary outcomes. Levels of missing data will be reported along with any systematic occurrences of missing data observed in the datasets.

To avoid loss of efficiency missing outcome values (both primary and secondary SWEMWBS) will be estimated using baseline observation carry forward (BOCF), if the proportion of missing data is greater than 5% and less than 40%. Where there is less than 5% missing data, the proportion of missing data is considered negligible and missing observations will be excluded. If more than 40% of the primary outcome data are missing per protocol in the primary analysis the assumptions are less plausible. The interpretative limitations of the data will be discussed in the results section, where this is the case.

7.5 Data review

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

7.6 Primary analysis

The primary analysis will be analysis by treatment allocated (i.e. oACT versus NoACT), including all available data for participants (ATA dataset).

Quantity of alcohol consumed (AC) in the 28 days prior to the 6-month follow-up assessment will be analysed using analysis of covariance (ANCOVA) to compare the mean response across treatment groups, with fixed effects for treatment group, age, ethnicity and gender. The outcome will be adjusted for baseline by including the baseline measure as a covariate. Results will be presented as mean differences between treatment and control groups, with accompanying 95% confidence intervals.

Diagnostic tests and plots to assess the assumptions of normality for AC will be performed prior to analysis. Where there are significant departures from the model, alternative models will be implemented based on the distribution of the data. If it is not possible to fit a suitable model, data will be transformed prior to analysis or the non-parametric Wilcoxon Rank Sum test will be used to compare the median response across treatment groups. Where non-parametric methods are used, the Hodges-Lehmann method for two independent samples will be used to compute non-parametric confidence intervals of the median difference.

7.7 Secondary analysis

The secondary outcomes SWEMWBS, PHQ-9 and GAD-7 will be analysed using ANCOVA to compare the mean response across treatment groups, with fixed effects for treatment group, age, ethnicity and gender. The outcome will be adjusted for baseline by including the baseline measures as a covariate. Results will be presented as mean differences between intervention and control groups, with accompanying 95% confidence intervals.

Secondary analysis will be performed for the Per Protocol analysis for the primary outcome and SWEMWBS at 6 months follow-up.

Exploratory regression analysis will be performed to model the relationship between prognostic indicators of outcomes and types of intervention delivered by the oACT and observed outcomes at 6-month follow-up, separately for the primary outcome and SWEMWBS. Prognostic indicators in this analysis will include age, gender, baseline AUDIT, APQ and SADQ.

Other secondary outcomes and outcomes derived from TLFB28, and demographic data, will be summarised to compare treatment groups. Means and standard deviations will be calculated for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables and frequencies and percentages for categorical variables.

7.8 Short-term health economic outcomes and analysis

The economic analysis will use data collected from individuals in intervention and control sites on healthcare resource use, in combination with cost estimates for each resource item, to compare healthcare costs between intervention and control sites.

7.8.1 Primary outcome - economic analysis

For these analyses the primary outcome will be estimated NHS costs.

7.8.2 Secondary outcomes - economic analysis

Secondary outcomes will be NHS resource use, wider community resource use, costs associated with wider community resource use (see section on CSRI) and the cost-effectiveness of oACTs calculated as cost per Quality-Adjusted Life Year (QALY) gained compared to control. QALYs gained will be estimated using EQ-5D-5L.

7.8.3 Economic analyses

We will combine individual resource use data with item-level cost estimates to estimate the total NHS and wider community costs for each individual in the 6-months prior to the baseline assessment and the 6-months between baseline and follow-up. This outcome will be analysed in line with the primary analysis, using analysis of covariance (ANCOVA) to compare the mean costs across treatment groups, with fixed effects for treatment group, age, ethnicity and gender. The outcome will be adjusted for baseline by including the baseline measure as a covariate. Results will be presented as mean differences between treatment and control groups, with accompanying 95% confidence intervals.

Diagnostic tests and plots to assess the assumptions of normality for costs will be performed prior to analysis. Where there are significant departures from the model, alternative models will be implemented based on the distribution of the data. If it is not possible to fit a suitable model, data will be transformed prior to analysis or the non-parametric Wilcoxon Rank Sum test will be used to compare the median response across treatment groups. Where non-parametric methods are used, the Hodges-Lehmann method for two independent samples will be used to compute non-parametric confidence intervals of the median difference.

Cost-effectiveness, measured in costs per QALY gained, will be estimated by calculating the mean difference in costs accrued between the intervention and control group at follow-up and dividing by the mean difference in QALYs gained at follow-up.

7.9 Software

All statistical analysis will be conducted using Stata version 16.1 (upwards). Analysis and results will be presented in accordance with CONSORT guidelines (60).

8 Storage and handling of data and confidentiality

8.1 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.

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, their hospital 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 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.

Pseudonymised data will be downloaded from RCC by the HHTU data team following a fully auditable process in line with HHTU SOPs. Data outputs will be stored within a study specific secure data folder in the HHTU Box instance, which is within scope of the HHTU NHS Data Security and Protection (DSP) Toolkit. Only authorised research staff will be granted access for the purposes of reporting and statistical analysis.

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

An end of study notification will be sent to the sponsor before data is released via the University of Hull Data Safe Haven to the study statisticians, at the University of Kent, Canterbury, UK and the University of Sheffield, Sheffield, 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.

8.2 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 DSP Toolkit. Access to data systems will be controlled by the HHTU SOPs and is all activity is fully auditable. Granular role based permission will be assigned according to the study role.

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 by HHTU, the REC, local R&D Departments and the regulatory authorities.

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

9 Data Monitoring

The monitoring of data quality and completeness will be undertaken by HHTU according to the monitoring plan. As all data is captured electronically this approach is feasible and has been implemented across HHTU studies.

During the first days of recruitment and data collection, there will be more frequent monitoring of informed consent forms and study survey measure completeness to ensure that researchers are conducting the study properly. There will be ongoing remote monitoring of informed consent 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 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.

10 Safety Procedures and Reporting

10.1 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 policies.

10.1.1 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 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.

10.1.2 Follow-up Interviews:

All researchers will be trained on the lone working policy and will only arrange follow-up interviews in agreed clinical settings (i.e. hospital site outpatient department) or public spaces, or they will be conducted over the telephone or via video call. 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.

11 QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

11.1 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).

11.2 Patient and Public Involvement

The study team works closely with the ProACTIVE Patient and Public Involvement (PPI) Coordinator based at the Clinical Experimental Sciences, Department of Psychiatry, University of Southampton, and the associated Public Advisory Group. The input of PPI in this study has assisted in the development of a) the design of PIS and other participant study documents, b) the practical implementation of the study in hospital/follow-up; c) the appropriateness of inclusion and exclusion criteria; d) the researcher training requirements; and e) the delivery of the study survey measures.

11.3 Ethics Committee Approvals

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

The Sponsor (University of Hull) will be responsible for deciding whether amendments are substantial or non-substantial in collaboration with the Chief Investigator. Where an amendment 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 an amendment requires local approval, this shall be sought prior to the amendment being implemented in accordance with the categorisation given on the HRA approval letter. Should an amendment 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 amendments for logistical or administrative purposes may be implemented immediately. Amendments will be logged on the Sponsor Study Amendment 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.

11.4 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. Only clinical staff can notify researchers of the potential patient interest in participation, they 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 in conjunction with the ProACTIVE PPI Coordinator and Public Advisory Group, 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 form 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 leaflet developed in conjunction with research sites containing details of where to 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 relapsed 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 £10 voucher to compensate them for their time at the 6-month follow-up interview.

Language barriers: The study team felt it was not feasible due to budgetary constraints to include those who were unable to communicate sufficiently in verbal English, as it would not be possible to provide access to interpreters for a range of languages across the period of the study or to arrange follow-up interviews. In addition, many of the measures used in this study have only been validated in English.

Anonymised data and confidentiality: No research data collected in the study will be attributed to a named individual or their medical records. No information collected through the study survey measures will be communicated or transferred to clinical staff or the participant's medical record.

Researchers will remain blind to the total scores on measures other than those guiding inclusion and exclusion criteria. 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 highlighted 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 grossly intoxicated. 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 if Hull website and the website address will be contained within the PIS. Contact details for the ProACTIVE team are also included on the PIS in case participants wish to access the results in a different format.

11.5 Protocol Compliance

11.5.1 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.

In the event of doubt or for further information, the Investigator should contact the Trial Manager.

11.5.2 Archiving

Electronic RCC database records and site files will be archived in accordance with the HHTU Archiving standard operating 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.

11.6 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.

11.7 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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