Protocol title: A three-arm, Randomised Controlled Trial of the effectiveness and cost-effectiveness of adjunctive medication management and contingency management to enhance adherence to medications for relapse prevention in alcohol dependence

Protocol number:
Trial registration, trial id and registry name

Version	Date	Purpose/change
1.0	21/07/2015	
2.0	18/11/2015	Inclusion of a summary letter to participants receiving medication management
3.0	08/06/2016	Additional questions on emergency supply of acamprosate
4.0	02/05/2017	Extension of data collection window to 60 days at 6 and 12 month follow-up
5.0	20/06/2017	Removal of current dependence on cannabis use as an exclusion criterion.

Short title:	Alcohol Dependence and Adherence to Medicine (ADAM)
Protocol version:	5
Protocol date:	20th June 2017
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Contents

List of abbreviations

ADSUS = Adult Service Use Schedule

APQ = Alcohol Problems Questionnaire

AUQ = Alcohol Urge Questionnaire

ASSIST = Alcohol, Smoking and Substance Involvement Screening Test

BMQ = Beliefs About Medication Questionnaire

CIDI = Composite International Diagnostic Interview

CM = Contingency management

EQ-5D-5L – Health Related Quality of Life

MEMS = Medication Events Monitoring System

MM = Medication management

MMAS = Moriskey Medication Adherence Scale

SADQ = Severity of Alcohol Dependence Questionnaire

SS = Standard support

STAR = Scale to Assess the Therapeutic Relationship

TLFB = Timeline Follow Back

1. Summary of research

Design: 3-arm, prospective, pragmatic, randomised controlled, parallel group clinical trial of strategies to enhance adherence to prescribed acamprosate for alcohol dependence. Standard support (SS), SS with adjunctive medication management (SS+MM), SS and MM with adjunctive contingency management (SS+MM+CM). Outcome assessment will be at 6 and 12 months post randomisation.

Setting: Specialist community alcohol treatment services, community pharmacies local to participants and a central telephone support service.

Population: Abstinent alcohol dependent adults, suitable for prescription of acamprosate, willing and able to provide informed consent.

Inclusion criteria: Aged >=18, ICD-10 alcohol dependence, currently abstinent from alcohol, commencing a prescription for acamprosate.
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.

Heath technologies: MM provided by pharmacists via a central telephone support service (weekly for 6 weeks and then fortnightly for 6 weeks and then 4-weekly up to 24 weeks). MM plus CM: Small incentives (vouchers) will be provided to reinforce adherence to telephone support, ranging from £2 to £10 for each MM session completed, with a total value of up to £120 for completing all support sessions.

Primary outcome measure: Proportion of prescribed medication taken assessed using Medication Events Monitoring System (MEMS) and cross-verified using pill count and self-report at 6 months post randomisation.

Secondary outcomes: Proportion of prescribed medication taken, estimated by self-report at 12 months post-randomisation. Total alcohol consumed, drinks per drinking day, percent days abstinent in standard drinks (1 standard drink = 8g ethanol) in the previous 90 days derived using the Time Line Follow Back Form 90. Time to first drink, relapse to any drinking and relapse to heavy drinking (8+/6+ UK units for males/females on a single occasion) derived from self-report. Alcohol related problems (Alcohol Problems Questionnaire), alcohol craving (Alcohol Urge Questionnaire) and severity of alcohol dependence. Measured at baseline, 6 and 12 months post-randomisation.

Process outcome measures: Participants' beliefs about medications (BMQ; measured at baseline and 6 month follow-up), the therapeutic relationship with the care provider (STAR: measured at 6 month follow-up) adverse events (measured at each bi-monthly research visit).

Economic outcome measures: Health related quality of life (EQ-5D-5L) and Adult Service Use Schedule modified for alcohol-misusing populations measured at baseline, 6 and 12 months post-randomisation. Costs associated with the provision of control and trial interventions, including costs associated with delivery, training, management and overheads.

Primary analysis: The primary analysis will be conducted using an intention-to-treat approach. As the study involves three arms, the initial step of the primary analysis will use a multiple analysis of

covariance, adjusted for stratification factors, to explore for overall effects between the three arms. If evidence of effect is observed a second analysis, using an analysis of covariance, will explore the mean differences in the primary outcome by comparing SS versus SS+MM and SS versus SS+MM+CM. All results will be presented with estimates of precision and associated 95% confidence intervals.

Economic analysis: Analysis of the costs and effects of MM with or without CM for alcohol dependence compared to SS. The primary economic perspective will be the health and social care provider perspective. Broader perspectives will be considered in sensitivity analyses (i.e. criminal justice contacts and criminal activity, patient and family costs).

Sample size: Differential allocation of the order of 2:1:1 to maximize the utility of resources with twice as many being allocated to the SS group than the intervention groups. A clinically important difference in adherence to medication is estimated as an effect size of the order of 0.3. To estimate this difference using power of 80%, alpha 0.05 with a 2 sided test requires 524 analysed at 6 months post-randomisation across the three groups. Allowing for attrition of 30%, less than observed in other trials in similar populations, requires a total sample size at allocation of 748; 374 allocated to SS, and 187 each to SS+MM and SS+MM+CM. In addition to addressing the primary outcome the sample size is sufficient to identify a clinically important difference effect size of 0.3 for alcohol consumption measures at both 6 and 12 months post randomization.

Allocation: Participants will be allocated following informed consent to take part and within one month of initiation of acamprosate. Allocation will be stratified by site, severity of alcohol dependence and the prescription of any other relapse prevention medication. As a pragmatic study interventionists will be unblended with regard to participant allocation but follow-up assessments will be conducted blind.

2. Trial Management Group

The programme will be managed by a Trial Management Group (TMG) chaired by the Chief Investigator and will include all co-investigators and service user representatives. Collaborators will be included as required. The TMG will meet on a monthly basis throughout the course of the programme, either face to face or by teleconference.

3. Trial Steering Committee

The TMG will report to an independent Trial Steering Committee (TSC) which will be convened on an annual basis as a minimum to approve the protocols and monitor the progress of the trial.

4. Data Monitoring and Ethics Committee

An independent Data Monitoring and Ethics Committee will convene on an annual basis as a minimum to review the trial data and make recommendations to the TSC and TMG based on the ethical conduct and safety of the research.

5. Background and rationale

Alcohol misuse is a global problem and is the third leading cause of disability in Europe (1). In the UK, there has been a consistent, year on year increase in harm related to alcohol. Alcohol-related NHS hospital admissions have more than doubled since 2002/03, with an estimated 1,220,300 admissions related to alcohol in 2011/12 (2). Chronic health conditions related to alcohol have increased in prevalence in the UK, including liver cancer, pancreatitis, alcoholic liver-disease and alcohol use

disorders (3). Mental health may be negatively affected by the chronic, heavy use of alcohol with increased risk of depression, anxiety, suicidality, psychosis and impairments to memory and other cognitive functions. Alcohol may contribute to social problems such as unemployment, criminality, martial breakdown, and domestic violence (4-7). The physical, mental and social problems associated with alcohol place a considerable burden on the UK economy. The estimated cost to the UK economy is £21 billion annually [18], of which the NHS costs are estimated at £3.5 billion (8).

The prevalence of alcohol dependence in the UK is estimated at 9.3% of men and 3.6% of women (9). The number of people entering specialist alcohol treatment has increased each year between 2008, when the Department of Health began collecting data, and 2012 (10). The number successfully completing treatment has also risen over the same reporting period but the majority of those dependent on alcohol undergo frequent episodes of withdrawal and resumption of drinking, as many as 70% of service users relapse in the first 12 months post treatment (11, 12). Improved treatment for alcohol dependence has been identified as a priority in the UK Government's Alcohol Strategy (8). Providing effective treatment for alcohol dependence to reduce relapse rates and therefore alcohol associated harms will contribute to this objective.

5.1 Acamprosate for relapse prevention in alcohol dependence

NICE recommends the use of acamprosate in combination with a psychological intervention as first-line treatments for relapse prevention in moderate to severe alcohol dependence (13). Acamprosate Calcium has been licensed for use in relapse prevention in alcohol dependence in the UK since 1995. Acamprosate is believed to modulate the glutamatergic system and stabilise the imbalance between inhibitory (GABA) and excitatory (glutamate) neurotransmitters in the brain consequent to the adaptations to chronic alcohol exposure thus reducing the conditioned effect of alcohol and the negative reinforcement of the addictive behaviour (14-16). Systematic reviews of the effectiveness of acamprosate found it to have a significant but moderate effect on maintenance of alcohol abstinence in clients with alcohol dependence (16, 17).

5.2 Adherence to acamprosate

Despite the therapeutic potential of acamprosate, adherence to the medication poses a problem for effectiveness in clinical practice. Medication adherence is a common problem across clinical care but is particularly an issue in chronic conditions and greater risk of poor adherence has been associated with substance misuse [32]. A meta-analysis of the effects of compliance on the efficacy of acamprosate in alcohol dependence found low rates of compliance (18), 69% of participants were at least 80% compliant from treatment initiation to the first post-baseline appointment at 15-30 days (early compliance) and 51% of participants were at least 80% compliant between the first post-baseline appointment to the end of treatment (late compliance). Examining the adherence rates to acamprosate of those clinical trials identified in the systematic review conducted by Donoghue et al., (19) (table 1) a wide variation between studies was identified, ranging from 28% up to 6 months in the only UK trial (20) to 94% in Portugal (21).

Several methods are used in clinical trials to monitor medication adherence. Swift et al., (22) suggest a hierarchy from low to high confidence in the method of adherence monitoring for naltrexone based on a patient's ability to evade measurement of adherence. Patient self-report, counting of returned medication or inspection of blister packs were assigned "low" confidence, electronic monitoring of pill bottle opening (Medication Events Monitoring System (MEMS) caps) or biomarkers such as the addition of riboflavin were assigned a "medium" confidence. "High"

confidence was assigned to supervised dosing, long-acting injectable preparations or monitoring of blood levels of the prescribed medication. Similar methods of adherence monitoring have been used in clinical trials for acamprosate (see Rösner et al., (16) for a review). In clinical practice some methods of adherence monitoring, such as supervised dosing and monitoring blood levels, may not be practical due to staff time, costs and practicality for service users, a combination of methods may therefore be advantageous. Further, no injectable preparation of acamprosate has been developed.

Suboptimal outcomes may result from underdosing, overdosing or taking medication at incorrect intervals (23). The impact of medication adherence on treatment effectiveness has been explored in several naltrexone trials for alcohol dependence. Results suggest better medication adherence is associated with improved outcomes (24-30). There has been comparably less work completed investigating the effect of adherence to acamprosate on alcohol outcomes. A recent analysis of the COMBINE study data found that poor adherence to both acamprosate and naltrexone was associated with lower percentage days abstinent and higher percent days heavy drinking (31). It was also found that those who were non-adherent early in the trial had poorer alcohol outcomes than those who were non-adherent later in the trial regardless of the medication prescribed.

5.3 Reasons for non-adherence

The reasons for non-adherence are complex and often due to multiple influences (32). The complexity of the dose regimen may influence adherence to medication with greater dose frequency and complexity of instructions associated with poorer adherence (33, 34). Comorbid depression is a predictor of poor adherence to prescribed medical treatments in those with chronic health conditions such as HIV and AIDS (35), diabetes (36) and coronary heart disease. Depression is common in patients with alcohol dependence (37) and may therefore be a contributing factor to poor adherence to pharmacotherapies for relapse prevention.

The experience of side-effects may contribute to non-adherence to medication for alcohol relapse prevention. Side-effects were the second most common reason for medication non-adherence (behind forgetting) in the COMBINE study of naltrexone and acamprosate (31). The combined therapy of acamprosate and naltrexone resulted in decreased adherence (defined as taking 80% or more of prescribed medication) compared to a single active therapy. It was reported that this may be due to the increase in side effects experienced by participants taking both medications (30). In addition, those who did not adhere to medication reported not only more side-effects but also a lack of benefit from the medication (31).

The Self-regulatory model (SRM) was conceptualised by Leventhal et al. (38) to help to explain illness related behaviour, including adherence to medications, in chronic illness. In the SRM a person's cognitive representation of their illness is associated with their subsequent coping behaviour, including adherence to medication. The model suggests that the person is an active 'problem solver' and their coping behaviour represents a common sense response to their interpretation of their experience and knowledge of their illness. Horne (39) expanded this model to explain treatment adherence to include specific treatment beliefs. It is proposed that patients' adherence decisions are based on an assessment of the costs and benefits (40). A person's beliefs about the necessity of the medication for improving or maintaining their health are weighed against the person's concerns about the potential adverse effects of the medication. In chronic health conditions such as asthma, diabetes, cardiac disease and cancer, a greater perception of the benefits of a medication is associated with greater adherence, and greater concern about adverse effects of a medication is associated with poorer adherence (40, 41). The development of effective interventions to improve patients'

uncertainties about the necessity for medication and concerns about the potential adverse effects is a priority to enhance adherence in chronic health conditions (23, 41)

5.4 Medication management

The NICE alcohol treatment guidelines (13) recommend that service users prescribed acamprosate or naltrexone "…should stay under supervision, at least monthly, for 6 months, and at reduced but regular intervals if the drug is continued after 6 months" p456. In NHS clinical practice the frequency and content of support is delivered by a combination of different agencies including primary care and specialist alcohol services.

Psychosocial interventions to support improved adherence to pharmacotherapies for alcohol dependence have the potential to promote positive beliefs about medication and address concerns. BRENDA is a manualised intervention (42) designed for use by health care professionals and has been used in several clinical trials (43-46). BRENDA is a 6 stage intervention and is an acronym for these stages; Biopsychosocial evaluation, Report, Empathy, Needs assessment/goals, Direct advice, and Assessment. BRENDA has been found to be beneficial for improving adherence to naltrexone for alcohol dependence (47).

Medical Management is a manual based psychosocial intervention that was developed from BRENDA and other available MM interventions by Pettinati et al., (48) for the COMBINE study of naltrexone and acamprosate for alcohol dependence (24) and has been used in subsequent clinical trials of other medications (49, 50). Medical management aims to improve medication and psychosocial treatment adherence by providing education, support and practical advice to service users about their drinking behaviour and medication. The initial session lasts approximately 40-60 minutes, which acts as a foundation for the subsequent sessions which last approximately 15 to 30 minutes. The initial session includes information about the patient's diagnosis, identifies treatment goals, the rationale for taking the prescribed medication, information about the medication and a review of the dosing instructions, the rationale for adhering to the prescribed dose regimen and developing an individualised plan for maintaining adherence and discussing support groups participation. Alongside the calls, the participant will receive four summary letters over the 6 month period. The summary letters provide a visual reminder of the aims, goals and key information regarding their medication management plan. Despite the successful inclusion of psychosocial intervention to enhance adherence in clinical trials, there has been little research into its application in a more typical clinical setting.

5.5 The role of the pharmacist

There has been an increasing focus on the extension of the pharmacist's role beyond medication dispensing to improve public health (51-53), including their established role in HIV prevention in opioid addiction (54, 55), medicines use reviews (56) and supporting medicines adherence (57, 58). The delivery of MM to improve adherence to relapse prevention medication for alcohol dependence complements the expanding role of the pharmacy. In 2011 the Royal College of General Practitioners and the Royal Pharmaceutical Society issued a joint statement which identified a role for suitably qualified pharmacists to contribute to care planning and treatment interventions in substance misuse (59). This has been followed by a recent report of the commission on the future models of NHS care delivered through pharmacy (60).

The Healthy Living Pharmacy (HLP) initiative recognises the significant role that community pharmacists should play in the reduction of health inequalities (61). HLP's have been successful and

the initiative is currently being rolled out across the UK. Alcohol misuse is one of the conditions targeted by the HLP. Prior research has found that pharmacists and support staff have positive attitudes towards providing extended services in alcohol and substance misuse when adequate training is provided (62, 63) and alcohol service users are willing to engage with the pharmacists for this role, viewing the pharmacy as an accessible and suitable place to discuss issues related to alcohol (64). There has also been an increased emphasis on more specialist pharmacist providing support via a central telephone support service for more complex health conditions, providing patients with access to pharmacists with greater expertise and with greater convenience than attending a local community pharmacy (65).

5.6 Contingency management

Engagement with psychological interventions and retention in treatment is often poor in alcohol dependence and is associated with poorer treatment outcome (66, 67). CM is based on the psychological theory of operant conditioning. Target behaviours (for example, attendance at therapy sessions, medication adherence, or abstinence from alcohol) are reinforced by consistently applying small rewards in the form of vouchers, money or prizes, when the target behaviour is achieved. There is a growing body of work using CM in the substance misuse field, showing improved treatment retention and engagement (47) as well as adherence to prescribed pharmacotherapies such as naltrexone for opiate relapse prevention, and improved uptake rates of hepatitis vaccination, tuberculosis screening and treatment, and adherence to prescribed HIV pharmacotherapy (68-70). A systematic review conducted by NICE (13) concluded that the research on CM in alcohol dependence is limited and recommended the need for further research in this area based on the compelling evidence in the substance misuse field (69). Three randomised controlled trials (47, 71, 72) for the effectiveness of CM in alcohol dependence treatment were identified by a systematic review conducted by NICE (13). All of these studies used a prize-based protocol with incentives of variable magnitude based on abstinence and/or treatment participation (47, 71, 72). Fixed monetary incentives or monetary incentives on an escalating scale may also be used, for example to improve tuberculosis treatment adherence in injecting opioid and cocaine users (73) and improving the number of doses of naltrexone taken in those with opiate dependence (74). Much of the literature on CM has been conducted in the US. However, recognition for the therapeutic potential of CM is growing in the UK. A UK NIHR programme grant on CM in substance misuse, of which JS is the chief investigator, has found significant effects of CM on hepatitis B vaccination adherence and completion in injecting drug misusers (n=210) (75). Vaccination completion was just 9% in the treatment as usual group but significantly higher completion rates were found for both an escalating monetary incentive (49%), which began at £5 and increased by £5 after each completed vaccination and a fixed monetary incentive (45%) of £10 per completed vaccination.

5.7 Why this research is needed now

Alcohol dependence is a chronic condition and relapse is common following conventional psychosocial interventions (11, 12). The effectiveness of acamprosate in conjunction with psychosocial therapies for relapse prevention in alcohol dependence has been well documented (13, 16) such that routine prescribing of acamprosate in alcohol dependence in NHS services is recommended by NICE [6]. Its use in the UK has doubled between 2003 and 2012, including an 11% increase since publication of the NICE guidelines (76). Despite this, the impact of acamprosate is restricted due to poor adherence and insufficient duration of use. Supporting patients in using acamprosate correctly by

providing education about the benefits of acamprosate, its role in relapse prevention and possible side effects, and practical advice and support through the application of MM, has the potential to help improve adherence and increase the clinical effectiveness of acamprosate. However at present there is insufficient evidence as to which forms of intervention are effective in increasing acamprosate adherence to guide clinical practice. Hence, clinical trials of strategies to increase relapse prevention medication adherence were prioritised as a research recommendation by NICE (13).

The delivery of MM by pharmacists fits the framework for development and expansion of the role of the pharmacy proposed in the Royal Pharmaceutical Society's recent report (60) and also the HLP initiative. Pharmacists are ideally placed to deliver MM in this context. However the effectiveness of interventions to increase medication adherence for alcohol dependence delivered by pharmacists is currently not known.

CM has proven effectiveness to promote medication adherence in substance misuse, with adoption into NICE guidance and clinical practice in the UK (69). CM can be delivered at relatively low cost and without extensive training compared to other psychological and behavioural interventions (such as cognitive behaviour therapy or motivational enhancement therapy) but with greater clinical effectiveness in substance misuse. Financial incentives in CM are relatively modest (typically less than £10 per session) and can be delivered by staff with less training and clinical skill than required for other psychological interventions used in alcohol dependence, as the intervention follows a simple behavioural reinforcement schedule. There is currently a small but growing evidence base for CM in alcohol dependence, but if shown to be effective it has considerable potential to be adopted within NHS services and the pharmacy to enhance alcohol dependence treatment.

6. Aims and objectives

Aim:

1. To evaluate the acceptability, effectiveness and cost-effectiveness of adjunctive MM with and without CM in improving adherence to acamprosate for relapse prevention in alcohol dependence.

Objectives:

I. To conduct an internal pilot study to assess the feasibility, recruitment and acceptability of the proposed MM and CM interventions for pharmacists and service users.

II. To conduct a definitive three-arm, randomised controlled trial of the effectiveness of MM with and without CM compared to SS alone in enhancing adherence to acamprosate in alcohol dependence relapse prevention.

III. To estimate the cost effectiveness of MM with and without CM compared to SS alone in enhancing adherence to acamprosate in alcohol dependence relapse prevention.

IV. To assess the impact of adherence to acamprosate for alcohol dependence relapse prevention on abstinence and reduced alcohol consumption.

Primary effectiveness and cost-effectiveness hypotheses:

- MM and MM+CM will be more effective than SS alone in terms of the percentage of prescribed acamprosate taken, measured using the medication events monitoring system, supplemented by pill count and self-report at 6 months post-randomisation.
- MM and MM+CM will be more cost-effective than SS alone at 12 months post-randomisation.

Secondary hypotheses:

- MM and MM+CM will be more effective than SS in terms of the percentage of prescribed medication taken, measured using the medication events monitoring system, supplemented by pill count and self-report, at 12 months post-randomisation.
- Greater adherence to acamprosate will be associated with improved alcohol outcomes, namely a higher percentage of days abstinent, less units of alcohol per drinking day, longer time (latency) to first alcoholic drink, reduced relapse to any drinking and reduced relapse to heavy drinking at 6 and 12 months post-randomisation.
- Service user beliefs about medication, and therapeutic relationship with care providers, will moderate medication adherence at 6, and 12 months post-randomisation.

7. Method

7.1 Internal Pilot

An internal pilot phase will be conducted to demonstrate that recruitment, randomisation, the MM and CM interventions run as planned. This will include the practicability of recruiting of, on average, 11 participants per study site per month and delivery of MM and CM in by pharmacists based in a central telephone support service. The pilot phase design and methodology will be identical to the full trial. This will allow data collected during the pilot phase to be included in the statistical analysis of the primary and secondary outcomes after completion of the full trial as an internal pilot. This approach has been chosen as it is more cost effective and suitable for the proposed research. If the recruitment target is met and the trial proceeds, the participants in the pilot phase will be included in the final analysis, so maximising recruitment potential from the sites.

7.1.1 Design and theoretical/conceptual framework

The study will be a 3-arm, pragmatic, randomised controlled, parallel group clinical trial. Each participant will be prescribed acamprosate as soon as possible after alcohol abstinence is achieved for a minimum duration of 24 weeks. Follow-up contacts with the research team will take place 6 (+60 days) and 12 (+60 days) months post randomisation. Participants will collect their medication monthly from the community pharmacy, which will be dispensed form designated pharmacies in bottles with MEMSCaps. Consented participants will be randomised (in the order of 2:1:1) to receive;

- SS consisting of monthly pick up of prescribed acamprosate from the community pharmacy and monthly follow-up with their specialist alcohol team for three months followed by monthly follow up with their GP for three months; or
- SS+ MM once a week for the first 6 weeks, reducing to once a fortnight for the following 6 weeks, and then monthly for 3 months, delivered by telephone by a trained pharmacist from a central telephone support service; or
- SS+MM+CM which will include incentivisation for completion of each of the telephone MM support sessions, with the pharmacist.

7.1.1.1 Treatment arm 1: Standard support (SS)

All participants in the trial will be prescribed acamprosate (two 333mg tablets morning, afternoon and evening or two 333mg tablets in the morning and one 333mg tablet in the afternoon and evening if the service users body weight is below 60kg) as soon as possible following alcohol abstinence in addition to the psychosocial care normally provided. The decision to initiate acamprosate will be determined by the treating clinician in the specialist alcohol service in conjunction with the service user.

The NICE guideline on diagnosis, assessment and management of harmful drinking and alcohol dependence (13) recommends, "Service users taking acamprosate should stay under supervision, at least monthly, for 6 months, and at reduced but regular intervals if the drug is continued after 6 months" p426. In clinical practice, after completion of assisted alcohol withdrawal, service users remain under the care of the specialist alcohol service for up to three months before they are transferred back to the care of their GP for ongoing care including prescribing. The type, frequency and intensity of psychosocial intervention received vary between specialist alcohol services and between individual service users, dependent on their needs, local funding and services available. As this is a pragmatic RCT, SS will be the care normally provided by local participating services, and service use will be recorded for each participant. However, participating services have agreed to follow the NICE guideline with respect to acamprosate prescribing with trial participants. Based on the current service provision of the five proposed study centres, SS is monthly pick up of prescribed acamprosate from the community pharmacy and monthly monitoring of the service user for three months by the specialist alcohol service and then returned to the care of their GP for monthly monitoring in accordance with the NICE guidelines (13) and current NHS clinical practice. As the trial is pragmatic it will be possible for patients to continue being prescribed acamprosate beyond the 24 week period of medication adherence monitoring providing this is agreed between patients and clinicians, in accordance with NICE guidelines.

7.1.1.2 Treatment arm 2: Standard support plus medication management (SS+MM)

Participants will follow the same care pathway as those in the SS arm of the trial with the addition of MM, which will be delivered by a central telephone support service by trained pharmacists. The MM intervention will be adapted from the Medical Management intervention developed by Pettinati (48) for the COMBINE study, a randomised controlled clinical trial of naltrexone and acamprosate for alcohol dependence. A freely available comprehensive manual has been published by the research group. This will be used as a basis for the MM intervention for the proposed research. Adaptation has been made in consultation with service users and pharmacists to ensure that it is suitable and acceptable in the context of a UK central pharmacy telephone support srevice, delivered by trained pharmacists.

Medical Management in the COMBINE study was delivered once a week for the first 6 weeks, reducing to once a fortnight for the following 6 weeks, and then monthly for three months. The current study will follow the same schedule and the MM will be delivered by telephone by a trained pharmacist based in a central telephone support service in the UK provided by Celesio. The initial MM session will last approximately 30-45 minutes and will act as a foundation for the subsequent sessions, which will last approximately 10-15 minutes each. Each participant will be assigned a specific pharmacist based in the central telephone support service who will deliver each of the MM sessions for that participant where possible. The pharmacist will call the participant to deliver the MM session at an agreed time and a text message reminder will be sent the day before the appointment.

MM will provide support in developing strategies to help participants to manage their medication including the rationale for taking acamprosate, adhering to the dose regimen and managing side effects, education about their medication and alcohol dependence, and supporting participants' efforts to change their drinking behaviours. Treatment goals will be identified to tailor the intervention to the participant and an individual plan for maintaining adherence will be developed with the participant in the initial session to guide successive MM sessions. Over the 6 month period the

pharmacist will send four summary letters to the participant highlighting the participant's individual aims, goals and key information regarding their medication management plan.

7.1.1.3 Treatment arm 3: Standard support plus medication management with contingency management (SS+MM+CM)

Although available evidence suggests that MM enhances adherence to prescribed medication for relapse prevention in alcohol dependence, there is concern that attendance at MM sessions may be sub-optimal (77). To optimise attendance, participants will follow the same care pathway as those in the SS+MM arm of the trial but with the addition of CM. Incentives in the form of vouchers (not redeemable for alcohol) will be provided to reinforce attendance at MM sessions by telephone with the pharmacist. The CM procedure and value of the incentives has been informed by the available literature on CM in substance misusers (69) and alcohol dependence (13) and focus gorups with service users with experience with treatment services for alcohol dependnece. Participants will receive between £2 and £10 in the form of a voucher for each MM session completed, with a total value of up to £120 for completing all support sessions. After each MM session a SMS text message will be sent to the participant to inform them that they have been awarded a voucher, the magnitude of the voucher and the total voucher value received to date.

7.1.1.4 Intervention training

All pharmacists delivering the MM and CM interventions will receive adequate training, specifically designed for the study, prior to commencement of delivery of the interventions and will cover all aspects of the research protocol and the medication management and contingency management protocols.

7.1.2 Target population

The population will be currently abstinent alcohol dependent adults within the first month of prescription of acamprosate and who are both willing and able to provide informed consent to take part in the research.

7.1.3 Inclusion/exclusion criteria

Inclusion and exclusion criteria have been selected so that the sample population will be broadly representative of the target population as a whole. The decision to prescribe acamprosate will be made by the service users treating clinician in the conjunction with the service user, the research team will not be part of this decision.

7.1.3.1 Inclusion criteria

- Adult aged >= 18 years
- An ICD-10 diagnosis alcohol dependence,
- Currently abstinent from alcohol,
- Prescribed acamprosate by treating clinician
- Willing to provide informed consent to take part in the trial.

7.1.3.2 Exclusion criteria

- Severe physical/mental illness likely to preclude active participation in treatment or follow up,
- Current participation in another trial

- Unable to adequately understand verbal English
- Current dependence on an illicit substance (other than cannabis)

7.1.4 Setting/context

Participants for the current research will be recruited from specialist alcohol treatment services based in England. SS will be provided by these specialist services and the participants' General Practitioner as per current standard practice. MM and CM will be administered by pharmacists via a central telephone support service in the UK.

7.1.5 Sampling

Recruitment will take place for 3 months for the pilot phase of the trial, to assess recruitment rates.

7.1.6 Study entry

Following referral to the specialist alcohol service all service users who meet the inclusion criteria will be identified by the specialist alcohol service.

7.1.6.1 Informed consent

Potential participants will be initially contacted by a member of their specialist alcohol service to ask if they would be willing to speak with a member of the research team about the research trial. In addition, a poster advertising that the research is taking place will be placed in the participating specialist alcohol services to give service users the opportunity to express an interest in taking part with their key worker. A member of the research team will subsequently contact the service user to provide details of the nature and purpose of the research. If the service user expresses that they wish to continue with the research process a participant information sheet will be given. An information sheet will be given to the potential participant. An initial assessment appointment will be made at least 24 hours after the study information sheet has been given to allow time to consider the information and ask any questions. 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.

7.1.6.2 Initial assessment

All inclusion criteria will be reviewed and a diagnosis of alcohol dependence according to ICD-10 criteria will be confirmed using the Composite International Diagnostic Interview (CIDI; (78)). The suitability of service users for prescription of acamprosate will be determined by the treating clinician of the specialist alcohol service including clinical assessment and blood investigations according to NICE guidelines. Exclusion criteria will be assessed through interview with the participant to ensure that the service user is suitable to take part in the trial. Participants will be randomised following consent and initial assessment.

Acamprosate will be initiated by the specialist alcohol service in line with the normal clinical practice for the community alcohol service. Prescriptions will be dispensed monthly so that adherence data can be regularly collected by the research team and to ensure reduced loss of MEMS data. The prescription of acamprosate will be made in line with the normal care pathway, the responsibility for which normally transfers from the specialist alcohol team to the persons GP after three months.

7.1.7 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 whether or not to take part in the research and they are free to withdraw at any time without providing a reason for them doing so. Data collected up to the time of withdrawal will be used as appropriate unless the participant wishes for their data not to be used and will therefore be destroyed. Withdrawn subjects will be replaced as far as possible within the constraints of the duration of recruitment. The decision to continue to prescribe acamprosate throughout the trial will be made by the treating clinician in conjunction with the participant. If the decision not to continue prescribing/taking acamprosate is made at any stage of the trial participants will not be withdrawn from the trial and outcomes will still be collected.

7.1.8 Alcohol abstinence

If participants resume alcohol consumption during the trial period this will not exclude them from any aspect of taking part in the trial.

7.1.9 Randomisation

The proposed trial involves differential allocation of the order of 2:1:1 to maximize the utility of resources with twice as many being allocated to the SS group than the intervention groups. Randomisation will be carried out after consent has been gained and the initial baseline assessment has been conducted. A remote randomisation procedure will be used through an online system developed and maintained by Codeface Ltd to generate the treatment allocation, which will be initiated by a trained researcher. It is not possible for participants and the study team to be blind to treatment allocation. Allocation will employ a stratified random permuted block method with stratification by severity of alcohol dependence (SADQ score of <=30 or >30), site and the prescription of other relapse prevention medication. These variables are known to be related to clinical outcomes and will be collected at preliminary screening.

7.1.10 Data collection

Table 1 outlines the study outcome measures and timing of their administration during the study. Research and personal data will be collected using electronic data capture, specifically designed for this research study by Codeface Ltd, using a laptop computer. Laptop computers will be password protected. Data will be entered and saved on a secure server with a 256bit encryption, no data will be saved directly onto the laptop computer. Research data will be annoymised by assigning each participant a unique ID number, personal data will be stored separately to the research data to maintain participant anonymity.

All of the study interventions will be audio recorded and a proportion will be reviewed by the research team to check the fidelity of the delivery of the intervention and inform further training. Audio files will be stored on a secure server with restricted access through password protected computers. Consent to take part in the research will be captured using an electronic consent form overseen by the researcher.

		Baseline	Bi-Monthly visit (months 1 to 6)	6 month follow-up	12 month follow-up
CIDI	Diagnosis of alcohol dependence	☒	☐	☐	☐
ASSIST	Psychoactive drug misuse	☒	☐	☐	☐
SADQ	Severity of alcohol dependence	☒	☐	☒	☒
AUQ	Current craving for alcohol	☒	☐	☒	☒
APQ	Presence of alcohol related problems	☒	☐	☒	☒
TLFB	Percentage of days abstinent and Units of alcohol per drinking day Time to first alcoholic drink Time to relapse to any drinking Time to relapse to heavy drinking.	☒	☐	☒	☒
BMQ	Beliefs about medication specific to their health and general medication beliefs	☒	☐	☒	☐
EQ-5D-5L	Health related quality of life	☒	☐	☒	☒
AD-SUS	Service use	☒	☐	☒	☒
STAR	Therapeutic relationship with pharmacist delivering MM	☐	☐	☒	☐
MMAS	Assess self-reported adherence to acamprosate	☐	☐	☒	☒
MEMS	Percentage medication taken as prescribed	☐	☒	☒	☐
Pill count	Percentage of pills taken	☐	☒	☒	☐

Self-reported adherence	Percentage of pills taken Reasons for non-adherence	☐	☒	☒	☒

Table 1: Trial outcome measures, timing of administration and duration of participant completed questionnaires

7.1.10.1 Primary outcome measure

The primary outcome measure will be the percentage of medication taken as prescribed during the 24 weeks target phase of prescribing, post randomisation. The prescription of AC will be two tablets (333mg per tablet) three times a day (morning, afternoon and evening) total daily dose 1998mg) or two tablets in the morning and one tablet in the afternoon and evening (total daily dose of 1665mg) if the service user weighs less than 60kg. Participants will be instructed to take their medication in the morning between 6am and 11am, afternoon between 12pm and 4pm and evening between 5pm and 10pm. If the participant takes the prescribed dose (i.e. two tablets) within the specified time frame, this will be considered adherent. The percentage of medication taken as prescribed will be calculated from the total number of doses taken in relation to the total number of possible doses. Over the 24 week period the maximum number of prescribed doses of acamprosate is 504.

There is no definitive, gold-standard method to determine medication adherence, therefore a triangulated approach will be used with three methods of data collection. The Medication Events Monitoring System (MEMS) has been chosen due to its validity in measuring adherence and it will allow the collection of data relating to the time that the medication was taken (34). MEMS has been used in many clinical trials of adherence to medication for both mental and physical health (34) and alcohol dependence (50, 79-84). In addition pill count and self-report have been chosen as they are the most frequently used in clinical trials and can be implemented into clinical practice (23).

MEMSCap is a trademarked product of MWV Corporation. Microcircuits are integrated into medication bottle caps, which record the time and date when the vial is opened. MEMS software will be purchased to enable the data to be transferred to the trial team's computer system. A participant's MEMSCaps can be reset to allow a new prescription of the trial medication to be dispensed using the same bottle cap, thus minimising costs. All trial participants will be given monthly prescriptions of acamprosate, which will be dispensed on a monthly basis at the designated pharmacy. Participants will be asked to notify the research team if the MEMSCap is lost or broken and it will be replaced as soon as possible. Pill count will also be carried out by the pharmacist to measure adherence to acamprosate. When the participant's prescription is being dispensed, the pharmacists will record the number of pills returned. Participants will be seen bi-monthly by the research team so that the data from the MEMSCaps can be transferred and any issues with the MEMSCaps can also be identified at this stage. Researchers will also ask whether participants have received any other supply in addition to the prescribed acamprosate in the bottle with the MEMSCap – for example emergency supply of acamprosate from a pharmacist (in line with Medicines, Ethics and Practice emergency supply procedures). Participant self-report will be used to measure adherence by estimating the proportion of medication taken in the previous month. An algorithm has been developed to define the method of combining the three adherence measures into a single measure of adherence based on Swift et al. (22). MEMS is considered a measure which can be interpreted with 'medium' confidence and pill count and self-report are considered to be 'low' confidence measures of adherence. In cases of discrepancy between methods of adherence measurement or if data is missing, the data recorded by MEMS will be taken first, followed by pill count if MEMS is not available, and self-report if both MEMS and pill count data are not available. As part of our analysis we will investigate the concordance between these three measures. If all methods of adherence measurement are missing, participants will be considered to be non-adherent for the reporting period (previous one month).

7.1.10.2 Secondary outcome measures

At baseline assessment participant demographics will be collected as well as a history of use of acamprosate, other relapse prevention medication use, and previous medically assisted detoxification using a medical history checklist devised specifically for the trial. The substance use section of the Alcohol, Smoking and Substance Involvement Screening Test- Lite (ASSIST-Lite;(13)) will be administered to obtain a history of any substance use.

Severity of dependence will be measured at the initial screening assessment and at 6 and 12 month follow-up using the Severity of Alcohol Dependence Questionnaire (SADQ) (85). The SADQ is a 20-item self-complete 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.

Alcohol consumption will be measured using the Time Line Follow Back (TLFB) Form 90 (86), administered at initial screening assessment and at 6 and 12 month follow-up after initiation of acamprosate. Percentage days abstinent, units of alcohol per drinking day (1 UK unit = 8g alcohol), time to first alcoholic drink, relapse to any drinking and relapse to heavy drinking (8+/6+ units for males/females on a single occasion) will be computed.

Participants' beliefs about medications will be assessed using the Beliefs about Medications Questionnaire (BMQ; (87)). The BMQ assesses an individual's beliefs about medication specific to them and their health, as well as their general beliefs about medication. This questionnaire will be administered at initial screening assessment and at 6 month follow-up. The measure will be used to evaluate the impact of MM on beliefs and concerns about medication and the association with adherence to acamprosate.

Participants will be asked to rate their therapeutic relationship with the care provider monitoring their medication adherence at each follow up point using the STAR rating scale (88). Therapeutic relationship (or alliance) has been found to predict clinical outcome across a range of mental disorders (89) including alcohol dependence (90). This will be used as an additional process measure to assess the impact of therapeutic relationship on medication adherence and clinical outcome.

Alcohol related problems will be assessed at initial screening assessment and then at 6 and 12 month follow-up, using the Alcohol Problems Questionnaire (APQ; (4)). The APQ is a 46-item questionnaire assessing potential problems with psychological, physical, social, legal, employment, relationships and parenting that may be experienced due to alcohol. The Alcohol Urge Questionnaire (AUQ) (91) assesses current urge for alcohol using eight items which cover three factors: desire for a drink (4 items); expectation of positive effect from drinking (2 items); and inability to avoid drinking if alcohol was available (2 items). This questionnaire will be administered at initial screening assessment and at 6 and 12 month follow-up.

Health related quality of life will be measured using the EQ-5D-5L and participants' use of services will be measured using the Alcohol and Drug Adapted Adult Service Use Schedule (AD-SUS). These measures will be used to assess the cost-effectiveness of MM and MM+CM compared to SS. These measures will be collected at baseline assessment and at 6 and 12 month follow-up.

Participants will be asked at each bi-monthly research visit whether they have experienced any side effects from the medication. In addition, reasons for non-adherence will be recorded.

7.1.11 Fidelity of intervention delivery

The fidelity of delivery of MM and CM will be assessed and its impact on acamprosate adherence and clinical outcomes will be examined. All MM sessions will be audio recorded. A random sample, stratified by pharmacists delivering the intervention, of 10% of all audio recordings of each

the MM and MM+CM interventions will be rated by at least 2 trained raters who will be members of the research team, using a checklist of required elements. The raters will be supervised by the post-doctoral research pharmacist and the trial manager, through regular meetings. The post-doctoral research pharmacist and trial manager will check 10% of the fidelity ratings completed by the raters. The information gained from checking the raters fidelity ratings will be fed back to the raters during the regular supervision meetings to ensure as much accuracy as possible of the fidelity rating. The information from the fidelity checks will be fed back to the pharmacists delivering the MM and CM to improve intervention fidelity.

7.1.12 Success indicators

At the end of the pilot phase descriptive analysis will be undertaken to assess recruitment rates in each of the study sites over the first 3 months. These will be assessed against initial targets of recruiting on average 11 participants per month per site. The criterion for proceeding to the full trial will be achieving a recruitment rate of 55 participants per month across the 5 sites at least during the last month of the pilot phase. A higher recruitment rate has been set for the pilot phase of the trial, which has been calculated based on the average number of patients who complete detoxifications at the 5 trial sites (approximately 291 detoxifications per month across the 5 sites) and the clinical and research experience of the co-applicants. It is anticipated that after an initial lag in recruitment while the trial is being established, recruitment rates will increase. However, this high rate may not be maintained throughout the trial as it is dependent on a continual throughput of new patients through the treatment services, resulting in an average of 6 participants per site per month at the trial conclusion.

7.2 Definitive three arm trial

7.2.1 Sampling

The same participant selection method and method of randomisation will be used for the definitive trial as described for the pilot phase, in section 7.1.

7.2.2 Sample size

A clinically important difference in adherence to medication is estimated as an effect size of the order of 0.3. A recent meta-analysis (92) identified a larger effect size for acamprosate versus placebo when converted to drinking outcomes of the order of 0.4, with a number of studies reporting larger effects. In addition a major issue mediating the potential effect of acamprosate relates to adherence with very low rates reported in UK trials. This effect translates to what is considered a clinically important difference in mental health interventions in terms of a numbers needed to treat of 8, in that if any intervention strategy is found to be superior 8 participants would need to be treated to create an additional participant who is abstinent. As with all pragmatic studies final interpretation will be based upon actual effects observed and the integration of economic outcomes, but an effect size of less than 0.3 is unlikely to be clinically important.

To estimate this difference using power of 80%, alpha 0.05 with a 2 sided tested and differential allocation of 2:1:1 requires 524 analysed at the primary end-point, 6 months across the three groups. Allowing for attrition of 30%, less than observed in other trials in similar populations, requires a total sample size at allocation of 748; 374 allocated to SS, and 187 to SS+MM and 187 to SS+MM+CM. In addition to addressing the primary outcome the sample size is sufficient to identify a clinically

important difference effect size of 0.3 in alcohol consumption measures at 6 and 12 months post-randomisation.

7.2.3 Data collection

Data will be collected in accordance with the methods detailed in section 7.1.

7.2.4 Data analysis

In the main trial the primary outcome measure is percent prescribed medication taken at 24 weeks post-randomisation assessed using a triangulation method. After checking for distributional assumptions and employing necessary transformations, an initial multiple analysis of covariance will be undertaken using a mixed model approach addressing the observed differences between SS versus SS+MM versus SS+MM+CM. If this analysis provides evidence of effect a second analysis of covariance will explore the differences of SS versus SS+MM and SS versus SS+MM+CM. Covariates included in the analysis will include stratification variables, gender and body weight (<60kg or 60+ kg). Mean differences between the groups will be presented with associated 95% confidence intervals. Multiple imputation will be employed to address the nature of missing data and sensitivity analysis will address the influence of missing data on the observed outcome. Secondary analysis will address drinking outcomes at 6 and 12 months using appropriate modelling approaches and these will be adjusted for known confounders; SADQ, site, age and gender. Time to relapse and relapse to heavy drinking will be assessed using survival analysis. Further secondary analyses will explore adherence data at 12 months. We will explore the association between adherence and drinking outcomes using a linear regression adjusted for known confounders and include an adherence*allocation interaction term. As with most trials the analysis plan will be refined throughout the course of the study and the final analysis plan prepared and agreed by the research team and Trial Steering Committee.

Further analysis will be conducted to identify interactions between variables, including ratings of therapeutic relationship, and fidelity of MM and CM delivery, on clinical and adherence outcomes. The analysis will be governed by an explicit data analysis plan agreed in advance by the Trial Steering Committee.

7.2.5 Economic analysis

The economic evaluation will compare the costs and effects of SS+MM+CM and SS+MM compared to SS alone for adherence to acamprosate prescribed for alcohol dependence. The primary analysis will compare costs and cost effectiveness at 12 month follow up of (a) SS compared to SS+MM, and (b) SS compared to SS+MM+CM, in line with primary aims of the study. Secondary analyses will explore SS compared to SS+MM compared to SS+MM+CM in a three-way comparison. The primary economic perspective will be the health and social care provider (NHS/PSS). Broader patient and societal perspectives will be considered in sensitivity analysis (i.e. criminal justice contacts and criminal activity, patient travel costs). A cost-utility analysis will be conducted using quality-adjusted life-years (QALYs) based on the EQ-5D-5L, a more sensitive version of the EQ-5D, that is a measure of health-related quality of life extensively used in previous alcohol studies in the UK (e.g. UKATT Research Team (93)). QALYs will be calculated by estimating the area under the curve between each consecutive follow up point. Patient-level resource use will be collected using the Adult Service Use Schedule (ADSUS) modified for alcohol misuse (94) and treatment adherence from clinical records. The ADSUS includes items on the cost of crime. Resource use will be valued using national tariffs (PSSRU, NHS National Reference Costs). Costs and QALYs will not be discounted as the trial time horizon is 12

months. Costs and QALYs will be adjusted for pre-specified baseline covariates (age, gender, alcohol dependence severity) including costs and utility values using generalised linear modelling methods. Missing cost and QALY data will be imputed using multiple imputation methods. Cost-effectiveness will be assessed by estimating incremental cost-effectiveness ratios (ICERs) (95). Interventions with ICERs below £20,000 per additional QALY are generally considered cost-effective by NICE. Decision uncertainty around cost and effectiveness estimates will be represented by cost-effectiveness acceptability curves (CEACs) generated using non-parametric bootstrap methods to account for non-normal joint distributions of costs and outcomes (96).

The costs and benefits of interventions for alcohol problems, such as alcohol-related complications and mortality, extend well beyond the usual time horizons of clinical trials. Lifetime costs and effects will be modelled using data observed in this trial (costs, QALYs, drinking outcomes) with appropriate observational data from long term cohorts (mortality, relapse rates) guided by published economic modelling methods (97, 98). Costs and QALYs in the model will be discounted as per NICE guidance at 3.5% per annum after the first year to reflect time preferences. We will conduct a systematic and critical review of the current literature reporting on modelling methods used in the context of cost-effectiveness analysis in alcohol interventions. The review will inform the structure and development of a model to estimate the long term cost-effectiveness of Medication Management (MM) and MM + Contingency Management (CM) compared to Standard Support and inform on data required to populate such a model. These data will include relapse rates; mortality and morbidity by drinking status, sex and age; treatment and disease costs; and health state utility values by drinking status. We will validate the model by running the trial data using other published models and comparing the results. The two models most likely to be relevant (the Sheffield Alcohol Policy Model and the York Drinking Patterns Model) both utilise Markov state transition models using drinking status (moderate, hazardous, harmful defined by alcohol consumption) compatible with our trial outcomes. The final model will apply the treatment effect observed at 12 months together with an appropriate relapse rate, to drinking status and associated mortality and morbidity rates, costs and QALYs. The primary outcome will be costs and QALYs over patients' lifetimes starting from the distribution of patients by drinking status, age and gender at 12 month follow up. Uncertainty in model inputs will be incorporated through probabilistic sensitivity analysis (PSA) where all inputs are randomly varied using probability distributions rather than mean values. One-way and multi-way sensitivity analyses will be used to explore structural and parameter uncertainty such as the impact of varying discount rates for QALYs and costs, and worst best case scenarios for long term compliance, relapse rates, treatment effect, treatment costs and potential subgroup analyses.

8. Storage of source data and confidentiality

There are three sources of data collection for the current research project.

a. Data collection by the research team.

Research and personal data will be collected using electronic data capture, specifically designed for this research study by Codeface Ltd, using a laptop or desktop computer with wireless (3G or WiFi) connection. Laptop computers will be password protected. Data will sent to a secure server with a 256bit encryption (SSL/https) connection, 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 anonymised research data to maintain participant anonymity.

b. Delivery of the intervention and data collection by pharmacists based in a central telephone support service

A secure electronic patient management system, developed and maintained by Partizan Health, will be used to facilitate delivery of the medication management and contingency management interventions. This is a Cloud based system, all data is stored in the UK and meets the European Medicines Agency and the Food and Drug Administration requirements for handling patient Identifiable Information. SSL Cryptography for the transmission of data to/from the application layer and also to/from the database. All data will be encrypted with AES CBC encryption on the database. All study data will be transferred securely to the research team either via encrypted memory stick/email or extracted directly from the patient management system by the research team.

c. Audio recording of the intervention delivery by Celesio

All telephone calls are audio recorded and securely stored by Celesio as part of routine practice. Audio files will be securely transferred to the research team via email or direct downloading of the files from Celesios system.

All audio files and participant data will be stored on King's College London's secure server accessible by the research team via password protected computers only.

Identifiable patient information will be accessed by the clinical staff and information will be passed on to the research team with the patient's consent. Consent to take part in the study will also be completed electronically, overseen by a trained researcher, participants will be given the opportunity to receive a copy of the consent form. All data for analysis will be stored under code numbers so that no personal data can be obtained from it. Members of the research team will have access to participants' personal data in order to establish contact for the follow-up interviews. This will be explained in the information provided to potential participants. At the end of the study arrangements will be made with the appropriate data repository service for transfer and preservation of the data in accordance with the principles agreed by the NHS/NIHR for the preservation and sharing of clinical data.

9. Publication policy

Publication of the trial results will be the responsibility of the chief investigator

10. Safety reporting

A Serious Adverse Event (SAE) is defined as an untoward occurrence that;

a. Results in death;
b. Is life threatening
c. Requires hospitalisation or prologation of an existing hospital stay;
d. Results in persistent or significant disability or incapacity;
e. Consists of a congenital anomaly or birth defect; or
f. Is otherwise considered medically significant by the investigator.

The Chief Investigator will report an SAE to the Research Ethics Committee (REC) who provided favourable ethical opinion within 15 days of becoming aware of the event if the event is related (that is, resulted from administration of any of the research procedures), and unexpected (that is, the type of event is not listed in the protocol as an expected occurrence).

If an urgent safety measure is required, the Chief Investigator will immediately by telephone and then in writing within 3 days inform the REC who gave favourable ethical opinion the reasons for the urgent safety measures and the plan for further action.

The Chief Investigator will report on the safety pf participants in annual progress report to the REC.

11. Ethical considerations

Regulatory approvals: The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996) and Good Clinical Practice (GCP) and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework (Department of Health, 2008). This protocol and related documents will be submitted for review to the appropriate Research Ethics Committee (REC) and R&D management approval will be gained for all trial sites before the commencement of the research.

Consent: All participants will be given written information about the trial including the risks and benefits of taking part. In line with GCP, participants will be given ample opportunity (i.e. at least 24 hours) to ask any questions about the trial and its procedures. Participants' right to decline participation and withdraw from the research without it affecting their clinical care will be made clear. Consent will be collected electronically by a trained researcher before any trial related procedures take place by a member of the research team. Participants will be given the opportunity to receive a copy of the consent form.

Prescription of acamprosate: The decision to prescribe acamprosate will be made by the treating clinician of the specialist alcohol service in conjunction with the service user as part of their treatment plan.

Study questionnaires: There may be some psychological discomfort resulting form completion of the trial specific questionnaires and interviews, for example, regarding alcohol habits and associated problems and psychiatric disorders. However, the potential benefit to the service users health of improved adherence to acamprosate outweighs any minor transient discomfort experienced from completing the questionnaires/interviews.

Contingency Management: Vouchers for retailers that are not licenced to sell alcohol will be provided as incentives in the CM arm of the trial.

Honorarium: At each research appointment (initial assessment, 6 and 12 month follow-up) all participants will be given £10 cash to compensate them for their time and travel expenses.

Researcher risks: There are potential risks of aggression in intoxicated patients. However, the researchers will be experienced in clinical research with this population and appropriate NHS and university risk management policies will be employed.

Confidentiality: Participants anonymity will be preserved throughout by the use of code numbers for all data collection. Data will be anonymised and be stored by secure means (password protected computers/laptops, locked filing cabinets in lockable offices in buildings with swipe assess and security

presence) in accordance with Good Clinical Practice and King's College London's Standard Operating Procedures.

Conflict of interest: All participants will have access to the standard care provided by the specialist alcohol health service, therefore participation will not have any detrimental effects on the care received by the patient. This will be made clear to potential participants prior to requesting informed consent.

Information about results of study: During initial interviews and informed consent, patients will be told that the findings of the research can be requested to be sent to them in their preferred way (e.g. post, email, telephone) and that they are welcome to contact the research team to discuss the findings and ask any questions they have regarding the research and their participation.

12. References

1. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. The Lancet. 2009; 373(9682): 2223-33.
2. Health and Social Care Information Centre. Prescription Cost Analysis England 2012: Prescription items dispensed in the community in England and listed alphabetically within chemical entity by therapeutic class. Available at: https://catalogueicnhsuk/publications/prescribing/primary/pres-cost-anal-eng-2012/pres-cost-anal-eng-2012a-reppdf. 2013.
3. Murray CJ, Richards MA, Newton JN, Fenton KA, Anderson HR, Atkinson C, et al. UK health performance: findings of the Global Burden of Disease Study 2010. The Lancet. 2013; 381: 997-1020.
4. Drummond DC. The relationship between alcohol dependence and alcohol–related problems in a clinical population. British Journal of Addiction. 1990; 85(3): 357-66.
5. Foster J, Powell J, Marshall E, Peters T. Quality of life in alcohol-dependent subjects–a review. Quality of Life Research. 1999; 8(3): 255-61.
6. Henkel D. Unemployment and substance use: a review of the literature (1990-2010). Current Drug Abuse Reviews. 2011; 4(1): 4.
7. Leonard K. Domestic violence and alcohol: what is known and what do we need to know to encourage environmental interventions? Journal of Substance Use. 2001; 6(4): 235-47.
8. HM Government. The Government's Alcohol Strategy. Available at http://ranzettatypepadcom/files/alcohol-strategy-2012pdf 2012.
9. McManus S, Meltzer H, Brugha T, Bebbington P, Jenkins R. Adult psychiatric morbidity in England, 2007: results of a household survey. Available at: http://wwwhscicgovuk/pubs/psychiatricmorbidity07. 2009.
10. Public Health England. Alcohol Treatment in England 2012-2013. Available at: http://wwwntanhsuk/uploads/alcohol2012-13pdf. 2013.
11. Brandon TH, Vidrine JI, Litvin EB. Relapse and relapse prevention. Annu Rev Clin Psychol. 2007; 3: 257-84.
12. Hunt WA, Barnett LW, Branch LG. Relapse rates in addiction programs. Journal of ClinicalPpsychology. 1971; 27(4): 455-6.
13. Ali R, Meena S, Eastwood B, Richards I, Marsden J. Ultra-rapid screening for substance-use disorders: the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST-Lite). Drug and alcohol dependence. 2013; 132(1): 352-61.

14. Cole J, Littleton J, Little H. Acamprosate, but not naltrexone, inhibits conditioned abstinence behaviour associated with repeated ethanol administration and exposure to a plus-maze. Psychopharmacology. 2000; 147(4): 403-11.
15. Littleton J. Acamprosate in alcohol dependence: how does it work? Addiction. 1995; 90(9): 1179-88.
16. Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews. 2010; 9.
17. Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, et al. Pharmacotherapy for Adults With Alcohol Use Disorders in Outpatient Settings A Systematic Review and Meta-analysis. Journal of the American Medical Association. 2014; 311: 1889-900.
18. Koeter MW, van den Brink W, Lehert P. Effect of early and late compliance on the effectiveness of acamprosate in the treatment of alcohol dependence. Journal of substance abuse treatment. 2010; 39(3): 218-26.
19. Donoghue K, Elzerbi C, Saunders R, Whittington C, Pilling S, Drummond C. The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence, Europe versus the rest of the world: a meta‐analysis. In: Addiction: 2015.
20. Chick J, Howlett H, Morgan M, Ritson B. United Kingdom Multicentre Acamprosate Study (UKMAS): a 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol. Alcohol and Alcoholism. 2000; 35(2): 176-87.
21. Sass H, Soyka M, Mann K, Zieglgansberger W. Relapse prevention by acamprosate: results from a placebo-controlled study on alcohol dependence. Archives of General Psychiatry. 1996; 53(8): 673.
22. Swift R, Oslin DW, Alexander M, Forman R. Adherence monitoring in naltrexone pharmacotherapy trials: a systematic review. Journal of Studies on Alcohol and Drugs. 2011; 72(6): 1012.
23. Nunes V NJ, O'Flynn N, Calvert N, Kuntze S, Smithson H, Benson J, Blair J, Bowser A, Clyne W, Crome P, Haddad P, Hemingway S, Horne R, Johnson S, Kelly S, Packham B, Patel M, Steel J. Clinical Guidelines and Evidence Review for Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence. National Collaborating Centre for Primary Care and Royal College of General Practitioners., 2009.
24. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence. JAMA: the journal of the American Medical Association. 2006; 295(17): 2003-17.
25. Chick J, Anton R, Checinski K, Croop R, Drummond DC, Farmer R, et al. A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. Alcohol and Alcoholism. 2000; 35(6): 587-93.
26. Monti PM, Rohsenow DJ, Swift RM, Gulliver SB, Colby SM, Mueller TI, et al. Naltrexone and Cue Exposure With Coping and Communication Skills Training for Alcoholics: Treatment Process and 1‐Year Outcomes. Alcoholism: Clinical and Experimental Research. 2001; 25(11): 1634-47.
27. Namkoong K, Lee B-O, Lee P-G, Choi M-J, Lee E. Acamprosate in Korean alcohol-dependent patients: a multi-centre, randomized, double-blind, placebo-controlled study. Alcohol and Alcoholism. 2003; 38(2): 135-41.
28. Pettinati HM, Volpicelli JR, Pierce Jr JD, O'brien CP. Improving naltrexone response: an intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. Journal of Addictive Diseases. 2000; 19(1): 71-83.
29. Volpicelli JR, Rhines KC, Rhines JS, Volpicelli LA, Alterman AI, O'Brien CP. Naltrexone and alcohol dependence: role of subject compliance. Archives of General Psychiatry. 1997; 54(8): 737.
30. Zweben A, Pettinati HM, Weiss RD, Youngblood M, Cox CE, Mattson ME, et al. Relationship between medication adherence and treatment outcomes: the COMBINE study. Alcoholism: Clinical and Experimental Research. 2008; 32(9): 1661-9.

31. Gueorguieva R, Wu R, Krystal JH, Donovan D, O'Malley SS. Temporal patterns of adherence to medications and behavioral treatment and their relationship to patient characteristics and treatment response. Addictive behaviors. 2013; 38: 2119-27.
32. Weiss RD. Adherence to pharmacotherapy in patients with alcohol and opioid dependence. Addiction. 2004; 99(11): 1382-92.
33. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clinical Therapeutics. 2001; 23(8): 1296-310.
34. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. Cochrane Database of Systematic Reviews. 2008; 2(2).
35. Starace F, Ammassari A, Trotta MP, Murri R, De Longis P, Izzo C, et al. Depression is a risk factor for suboptimal adherence to highly active antiretroviral therapy. Journal of Acquired Immune Deficiency Syndromes. 2002; 31: S136-9.
36. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. Archives of Internal Medicine. 2000; 160(21): 3278.
37. Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Archives of General Psychiatry. 2005; 62(10): 1097.
38. Leventhal H, Diefenbach M, Leventhal EA. Illness cognition: using common sense to understand treatment adherence and affect cognition interactions. Cognitive Therapy and Research. 1992; 16(2): 143-63.
39. Horne R. Representations of medication and treatment: advances in theory and measurement. Perceptions of health and illness London, UK: Harwood Academic. 1997: 155-88.
40. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. Journal of Psychosomatic Research. 1999; 47(6): 555-67.
41. Horne R, Chapman SCE, Parham R, Freemantle N, Forbes A, Cooper V. Understanding Patients' Adherence-Related Beliefs about Medicines Prescribed for Long-Term Conditions: A Meta-Analytic Review of the Necessity-Concerns Framework. PLOS ONE. 2013; 8(12): e80633. doi:10.1371/journal.pone.0080633.
42. Volpicelli J. Combining medication and psychosocial treatments for addictions: The BRENDA approach. Guilford Press, 2001.
43. Gastpar M, Bonnet U, Böning J, Mann K, Schmidt LG, Soyka M, et al. Lack of efficacy of naltrexone in the prevention of alcohol relapse: results from a German multicenter study. Journal of Clinical Psychopharmacology. 2002; 22(6): 592-8.
44. Monterosso JR, Flannery BA, Pettinati HM, Oslin DW, Rukstalis M, O'Brien CP, et al. Predicting treatment response to naltrexone: the influence of craving and family history. The American Journal on Addictions. 2001; 10(3): 258-68.
45. Oslin DW, Lynch KG, Pettinati HM, Kampman KM, Gariti P, Gelfand L, et al. A Placebo‐Controlled Randomized Clinical Trial of Naltrexone in the Context of Different Levels of Psychosocial Intervention. Alcoholism: Clinical and Experimental Research. 2008; 32(7): 1299-308.
46. Pettinati HM, Kampman KM, Lynch KG, Xie H, Dackis C, Rabinowitz AR. A double blind, placebo-controlled trial that combines disulfiram and naltrexone for treating co-occurring cocaine and alcohol dependence. Addictive behaviors. 2008; 33(5): 651-67.
47. Petry NM, Martin B, Cooney JL, Kranzler HR. Give them prizes and they will come: Contingency management for treatment of alcohol dependence. Journal of Consulting and Clinical Psychology. 2000; 68(2): 250.
48. Pettinati HM, Weiss RD, Miller WR, Donovan D, Ernst DB, Rounsaville BJ, et al. Medical Management Treatment Manual. A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence COMBINE Monograph Series. 2004; 2.

49. Mann K, Lemenager T, Hoffmann S, Reinhard I, Hermann D, Batra A, et al. Results of a double‐blind, placebo‐controlled pharmacotherapy trial in alcoholism conducted in Germany and comparison with the US COMBINE study. Addiction biology. 2013.
50. O'Malley SS, Robin RW, Levenson AL, GreyWolf I, Chance LE, Hodgkinson CA, et al. Naltrexone Alone and With Sertraline for the Treatment of Alcohol Dependence in Alaska Natives and Non-Natives Residing in Rural Settings: A Randomized Controlled Trial. Alcoholism: Clinical and Experimental Research. 2008; 32(7): 1271-83.
51. Anderson C, Blenkinsopp A, Armstrong M. The contribution of community pharmacy to improving the public's health: summary report of the literature review 1990–2007. Available at http://eprintsnottinghamacuk/1576/1/The_contribution_of_community_pharmacy_to_improving_the_public's_health_Evidence_Base_Report_7pdf. 2009.
52. Anderson P, Kaner E, Wutzke S, Wensing M, Grol R, Heather N, et al. Attitudes and management of alcohol problems in general practice: descriptive analysis based on findings of a world health organization international collaborative survey. Alcohol and Alcoholism. 2003; 38(6): 597-601.
53. Eades CE, Ferguson JS, O'Carroll RE. Public health in community pharmacy: a systematic review of pharmacist and consumer views. BMC Public Health. 2011; 11(1): 582.
54. Sheridan J, Manning V, Ridge G, Mayet S, Strang J. Community pharmacies and the provision of opioid substitution services for drug misusers: changes in activity and attitudes of community pharmacists across England 1995–2005. Addiction. 2007; 102(11): 1824-30.
55. Sheridan J, Strang J, Taylor C, Barber N. HIV prevention and drug treatment services for drug misusers: a national study of community pharmacists' attitudes and their involvement in service specific training. Addiction. 1997; 92(12): 1737-48.
56. Blenkinsopp A, Bond C, Celino G, Inch J, Gray N. Medicines use review: adoption and spread of a service innovation. International Journal of Pharmacy Practice. 2008; 16(4): 271-6.
57. Glynn LG, Murphy AW, Smith SM, Schroeder K, Fahey T. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database of Systematic Reviews. 2010; 3(3).
58. Vermeire E, Wens J, Van Royen P, Biot Y, Hearnshaw H, Lindenmeyer A. Interventions for improving adherence to treatment recommendations in people with type 2 diabetes mellitus. Cochrane Database of Systematic Reviews. 2005; 2.
59. Royal Pharmaceutical Society and Royal College of General Practitioners. Joint statement Breaking down the barriers-how community pharmacists and GPs can work together to improve patient care. Available at http://wwwrcgporguk/news/2011/july/gps-and-pharmacists-working-together-to-improve-patient-careaspx. 2011.
60. Smith J, Picton C, Dayan M. Now or Never: Shaping pharmacy for the future. In: The report of the commission on future models of care delivered through pharmacy. Royal Pharmaceutical Society, 2013.
61. National Pharmacy Association. Healthy living pharmacy: An overview. Available at http://wwwnpacouk/Documents/HLP/HLP_overview_1211pdf. 2011.
62. Dhital R, Whittlesea CM, Milligan P, Khan NS, Norman IJ. The impact of training and delivering alcohol brief intervention on the knowledge and attitudes of community pharmacists: a before and after study. Drug and Alcohol Review. 2013; 32: 147-56.
63. Scott J, Mackridge AJ. Pharmacy support staff involvement in, and attitudes towards, pharmacy‐based services for drug misusers. International Journal of Pharmacy Practice. 2009; 17(6): 325-32.
64. Dhital R, Whittlesea CM, Norman IJ, Milligan P. Community pharmacy service users' views and perceptions of alcohol screening and brief intervention. Drug and Alcohol Review. 2010; 29(6): 596-602.
65. Elliott RA, Barber N, Clifford S, Horne R, Hartley E. The cost effectiveness of a telephone-based pharmacy advisory service to improve adherence to newly prescribed medicines. Pharmacy World & Science. 2008; 30(1): 17-23.

66. Graff FS, Morgan TJ, Epstein EE, McCrady BS, Cook SM, Jensen NK, et al. Engagement and retention in outpatient alcoholism treatment for women. The American Journal on Addictions. 2009; 18(4): 277-88.
67. Simpson DD, Joe GW, Brown BS. Treatment retention and follow-up outcomes in the Drug Abuse Treatment Outcome Study (DATOS). Psychology of Addictive behaviors. 1997; 11(4): 294.
68. Lussier JP, Heil SH, Mongeon JA, Badger GJ, Higgins ST. A meta‐analysis of voucher‐based reinforcement therapy for substance use disorders. Addiction. 2006; 101(2): 192-203.
69. National Institute for Health and Care Excellence. Drug misuse: psychological interventions. National Institute for Health and Care Excellence, 2007.
70. Prendergast M, Podus D, Finney J, Greenwell L, Roll J. Contingency management for treatment of substance use disorders: A meta‐analysis. Addiction. 2006; 101(11): 1546-60.
71. Alessi SM, Hanson T, Wieners M, Petry NM. Low-cost contingency management in community clinics: Delivering incentives partially in group therapy. Experimental and Clinical Psychopharmacology. 2007; 15(3): 293.
72. Litt MD, Kadden RM, Kabela-Cormier E, Petry N. Changing network support for drinking: Initial findings from the Network Support Project. Journal of Consulting and Clinical Psychology. 2007; 75(4): 542.
73. Malotte CK, Hollingshead JR, Rhodes F. Monetary versus nonmonetary incentives for TB skin test reading among drug users. American Journal of Preventive Medicine. 1999; 16(3): 182-8.
74. Preston KL, Silverman K, Umbricht A, DeJesus A, Montoya ID, Schuster CR. Improvement in naltrexone treatment compliance with contingency management. Drug and Alcohol Dependence. 1999; 54(2): 127-35.
75. Weaver T, Metrebian N, Hellier J, Pilling S, Charles V, Little N, et al. Cluster randomised trial of contingency management: Do incentives increase completion of Hepatitis B (HBV) vaccination completion amongst people in treatment for heroin dependence? Lancet under invited revision.
76. Health and Social care Information Centre. Statistics on Alcohol: England 2013. Available at https://catalogueicnhsuk/publications/public-health/alcohol/alco-eng-2013/alc-eng-2013-reppdf. 2013.
77. Reid SC, Teesson M, Sannibale C, Matsuda M, Haber PS. The efficacy of compliance therapy in pharmacotherapy for alcohol dependence: a randomized controlled trial. Journal of Studies on Alcohol and Drugs. 2005; 66(6): 833.
78. Organization WH. Composite international diagnostic interview (CIDI), Version 1.0. Geneva, WHO. 1990.
79. Anton RF, Moak DH, Latham P, Waid LR, Myrick H, Voronin K, et al. Naltrexone combined with either cognitive behavioral or motivational enhancement therapy for alcohol dependence. Journal of Clinical Psychopharmacology. 2005; 25(4): 349-57.
80. Killeen TK, Brady KT, Gold PB, Simpson KN, Faldowski RA, Tyson C, et al. Effectiveness of naltrexone in a community treatment program. Alcoholism: Clinical and Experimental Research. 2004; 28(11): 1710-7.
81. Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA. Naltrexone in the treatment of alcohol dependence. New England Journal of Medicine. 2001; 345(24): 1734-9.
82. Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB. A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. Archives of General Psychiatry. 1999; 56(8): 719.
83. O'Malley SS, Sinha R, Grilo CM, Capone C, Farren CK, McKee SA, et al. Naltrexone and Cognitive Behavioral Coping Skills Therapy for the Treatment of Alcohol Drinking and Eating Disorder Features in Alcohol‐Dependent Women: A Randomized Controlled Trial. Alcoholism: Clinical and Experimental Research. 2007; 31(4): 625-34.
84. Petrakis IL, Poling J, Levinson C, Nich C, Carroll K, Rounsaville B. Naltrexone and disulfiram in patients with alcohol dependence and comorbid psychiatric disorders. Biological Psychiatry. 2005; 57(10): 1128-37.

85. Stockwell T, Sitharthan T, McGrath D, Lang E. The measurement of alcohol dependence and impaired control in community samples. Addiction. 1994; 89(2): 167-84.
86. Sobell LC, Sobell MB. Timeline follow-back. In: Measuring alcohol consumption: 41-72. Springer, 1992.
87. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychology and Health. 1999; 14(1): 1-24.
88. Mcguire-Snieckus R, McCABE R, Catty J, Hansson L, Priebe S. A new scale to assess the therapeutic relationship in community mental health care: STAR. Psychological Medicine. 2007; 37(1): 85-96.
89. Flückiger C, Del Re A, Wampold BE, Symonds D, Horvath AO. How central is the alliance in psychotherapy? A multilevel longitudinal meta-analysis. Journal of Counseling Psychology. 2012; 59(1): 10.
90. Ernst DB, Pettinati HM, Weiss RD, Donovan DM, Longabaugh R. An intervention for treating alcohol dependence: relating elements of Medical Management to patient outcomes with implications for primary care. The Annals of Family Medicine. 2008; 6(5): 435-40.
91. Bohn MJ, Krahn DD, Staehler BA. Development and initial validation of a measure of drinking urges in abstinent alcoholics. Alcoholism: Clinical and Experimental Research. 1995; 19(3): 600-6.
92. Maisel NC, Blodgett JC, Wilbourne PL, Humphreys K, Finney JW. Meta‐analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? Addiction. 2013; 108(2): 275-93.
93. UKATT Research Team. UKATT Research Team: Effectiveness of treatment for alcohol problems: findings of the randomised United Kingdom Alcohol Treatment Trial (UKATT). British Medical Journal. 2005; 331: 541-4.
94. Barrett B, Byford S, Crawford MJ, Patton R, Drummond C, Henry JA, et al. Cost-effectiveness of screening and referral to an alcohol health worker in alcohol misusing patients attending an accident and emergency department: a decision-making approach. Drug and alcohol dependence. 2006; 81(1): 47-54.
95. Van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E‐ratios alongside a clinical trial. Health economics. 1994; 3(5): 309-19.
96. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. The British Journal of Psychiatry. 2005; 187(2): 106-8.
97. Barbosa C, Taylor B, Godfrey C, Rehm J, Parrott S, Drummond C. Modelling lifetime QALYs and health care costs from different drinking patterns over time: a Markov model. International Journal of Methods in Psychiatric Research. 2010; 19(2): 97-109.
98. Purshouse RC, Brennan A, Rafia R, Latimer NR, Archer RJ, Angus CR, et al. Modelling the cost-effectiveness of alcohol screening and brief interventions in primary care in England. Alcohol and Alcoholism. 2013; 48(2): 180-8.