

## Adjunctive Medication Management and Contingency Management to enhance adherence to acamprosate for alcohol dependence

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# Abstract

## Adjunctive Medication Management and Contingency Management to enhance adherence to acamprosate for alcohol dependence: the ADAM trial RCT

Kim Donoghue<sup>1,2\*</sup>, Sadie Boniface<sup>2,3</sup>, Eileen Brobbin<sup>2</sup>, Sarah Byford<sup>4</sup>, Rachel Coleman<sup>5</sup>, Simon Coulton<sup>6</sup>, Edward Day<sup>7</sup>, Ranjita Dhital<sup>2,8</sup>, Anum Farid<sup>2,9</sup>, Laura Hermann<sup>2,5</sup>, Amy Jordan<sup>2,10</sup>, Andreas Kimergård<sup>2</sup>, Maria-Leoni Koutsou<sup>11</sup>, Anne Lingford-Hughes<sup>12</sup>, John Marsden<sup>2,13</sup>, Joanne Neale<sup>2</sup>, Aimee O'Neill<sup>14</sup>, Thomas Phillips<sup>5</sup>, James Shearer<sup>4</sup>, Julia Sinclair<sup>14</sup>, Joanna Smith<sup>14</sup>, John Strang<sup>2,13</sup>, John Weinman<sup>15</sup>, Cate Whittlesea<sup>16</sup>, Kideshini Widyaratna<sup>17</sup> and Colin Drummond<sup>2,13</sup>

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**Background:** Acamprosate is an effective and cost-effective medication for alcohol relapse prevention but poor adherence can limit its full benefit. Effective interventions to support adherence to acamprosate are therefore needed.

**Objectives:** To determine the effectiveness of Medication Management, with and without Contingency Management, compared to Standard Support alone in enhancing adherence to acamprosate and the impact of adherence to acamprosate on abstinence and reduced alcohol consumption.

**Design:** Multicentre, three-arm, parallel-group, randomised controlled clinical trial.

**Setting:** Specialist alcohol treatment services in five regions of England (South East London, Central and North West London, Wessex, Yorkshire and Humber and West Midlands).

**Participants:** Adults (aged 18 years or more), an *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision, diagnosis of alcohol dependence, abstinent from alcohol at baseline assessment, in receipt of a prescription for acamprosate.

**Interventions:** (1) Standard Support, (2) Standard Support with adjunctive Medication Management provided by pharmacists via a clinical contact centre (12 sessions over 6 months), (3) Standard Support with adjunctive Medication Management plus Contingency Management that consisted of vouchers (up to £120) to reinforce participation in Medication Management. Consenting participants were randomised in a 2 : 1 : 1 ratio to one of the three groups using a stratified random permuted block method using a remote system. Participants and researchers were not blind to treatment allocation.

**Main outcome measures:** Primary outcome: self-reported percentage of medication taken in the previous 28 days at 6 months post randomisation. Economic outcome: EuroQol-5 Dimensions, a five-level version, used to calculate quality-adjusted life-years, with costs estimated using the Adult Service Use Schedule.

**Results:** Of the 1459 potential participants approached, 1019 (70%) were assessed and 739 (73) consented to participate in the study, 372 (50%) were allocated to Standard Support, 182 (25%) to Standard Support with Medication Management and 185 (25%) to Standard Support and Medication Management with Contingency Management. Data were available for 518 (70%) of participants at 6-month follow-up, 255 (68.5%) allocated to Standard Support, 122 (67.0%) to Standard Support and Medication Management and 141 (76.2%) to Standard Support and Medication Management with Contingency Management. The mean difference of per cent adherence to acamprosate was higher for those who received Standard Support and Medication Management with Contingency Management (10.6%, 95% confidence interval 19.6% to 1.6%) compared to Standard Support alone, at the primary end point (6-month follow-up). There was no significant difference in per cent days adherent when comparing Standard Support and Medication Management with Standard Support alone 3.1% (95% confidence interval 12.8% to -6.5%) or comparing Standard Support and Medication Management with Standard Support and Medication Management with Contingency Management 7.9% (95% confidence interval 18.7% to -2.8%). The primary economic analysis at 6 months found that Standard Support and Medication Management with Contingency Management was cost-effective compared to Standard Support alone, achieving small gains in quality-adjusted life-years at a lower cost per participant. Cost-effectiveness was not observed for adjunctive Medication Management compared to Standard Support alone. There were no serious adverse events related to the trial interventions reported.

**Limitations:** The trial's primary outcome measure changed substantially due to data collection difficulties and therefore relied on a measure of self-reported adherence. A lower than anticipated follow-up rate at 12 months may have lowered the statistical power to detect differences in the secondary analyses, although the primary analysis was not impacted.

**Conclusions:** Medication Management enhanced with Contingency Management is beneficial to patients for supporting them to take acamprosate.

**Future work:** Given our findings in relation to Contingency Management enhancing Medication Management adherence, future trials should be developed to explore its effectiveness and cost-effectiveness with other alcohol interventions where there is evidence of poor adherence.

**Trial registration:** This trial is registered as ISRCTN17083622 <https://doi.org/10.1186/ISRCTN17083622>.

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# Contents

List of tables	xiii
List of figures	xv
List of abbreviations	xvii
Plain language summary	xix
Scientific summary	xxi
<b>Chapter 1 Introduction</b>	<b>1</b>
Background and rationale	1
<i>Acamprosate for relapse prevention in alcohol dependence</i>	1
<i>Adherence to acamprosate</i>	2
<i>Reasons for non-adherence</i>	2
<i>Medication Management</i>	3
<i>The role of the pharmacist</i>	3
<i>Contingency Management</i>	3
<i>Why this research is needed now</i>	4
Aims and objectives	4
<i>Objectives</i>	4
<i>Primary hypothesis</i>	5
<i>Secondary hypotheses</i>	5
<b>Chapter 2 Intervention development and pharmacist training</b>	<b>7</b>
Focus groups with service users and pharmacists	7
<i>Methods</i>	7
<i>Results</i>	8
Patient and public involvement	12
Developing the interventions	12
<i>Medication Management</i>	12
<i>Contingency Management</i>	12
Developing pharmacist training	13
<b>Chapter 3 Trial methods</b>	<b>15</b>
Design and theoretical/conceptual framework	15
<i>Treatment arm 1: Standard Support</i>	15
<i>Treatment arm 2: Standard Support plus Medication Management (SS + MM)</i>	15
<i>Treatment arm 3: Standard Support plus Medication Management with Contingency Management (SS + MM + CM)</i>	16
Study setting/context	17
Target population	17
Inclusion/exclusion criteria	17
<i>Inclusion criteria</i>	17
<i>Exclusion criteria</i>	17

Study entry and baseline assessment	17
Withdrawal of participants	17
Alcohol abstinence	18
Randomisation	18
Data collection and management	18
Outcome measures	18
<i>Secondary outcome measures</i>	18
Fidelity of intervention delivery	20
Sample size	20
Statistical analysis	20
<i>Analysis by treatment allocated</i>	21
<i>Complier average causal effects</i>	21
<i>Missing data</i>	22
<i>Statistical analysis methods</i>	22
Economic analysis	23
Safety reporting	23
Ethics and dissemination	23
Monitoring	23
Amendments	23
<i>Deviations from the statistical analysis plan</i>	24
<b>Chapter 4 Trial statistical analysis</b>	<b>27</b>
Primary outcome analysis	30
<i>Late follow-up sensitivity analysis</i>	32
<i>Missing primary outcome data</i>	32
<i>Complier average causal effects analysis</i>	32
Secondary outcome analysis	33
Summary of results	35
<b>Chapter 5 Health economic evaluation</b>	<b>37</b>
Methods	37
<i>Method of economic evaluation</i>	37
<i>Perspective</i>	37
<i>Time horizon</i>	37
<i>Outcomes</i>	37
<i>Economic model</i>	37
<i>Measurement of resources</i>	37
<i>Valuation of resources</i>	38
<i>Intervention cost</i>	38
<i>Data analysis</i>	40
Results	41
<i>Data completeness</i>	41
<i>Resource use</i>	41
<i>Interventions</i>	43
<i>Health and social care services</i>	43
<i>Alcohol relapse prevention medication</i>	43
<i>Crime</i>	44
<i>Costs</i>	44
<i>Primary cost-utility analysis</i>	44
<i>Secondary cost-utility analysis at 12 months</i>	47
<i>Secondary cost-effectiveness analysis at 6 months</i>	49
<i>Sensitivity analysis</i>	52
<i>Cost-effectiveness outcomes modelled over 20 years</i>	53

Summary of findings	54
<i>SS + MM + CM versus SS</i>	54
<i>SS + MM versus SS</i>	56
<i>Implications</i>	56
<b>Chapter 6 Discussion</b>	<b>57</b>
Key findings	58
<i>Recruitment and randomisation</i>	58
<i>Primary outcome analysis and sensitivity analyses</i>	58
<i>Secondary outcome analyses</i>	59
<i>Health economic analysis</i>	59
Consideration of possible explanations	60
Comparison with previous research	61
Strengths and limitations	62
Patient and public involvement	63
Conclusions	63
<i>Generalisability</i>	63
<i>Implications for health care</i>	63
<i>Implications for research</i>	64
<b>Acknowledgements</b>	<b>67</b>
<b>References</b>	<b>71</b>
<b>Appendix 1 Additional statistical output</b>	<b>83</b>



# List of tables

<b>TABLE 1</b> Characteristics of the service users who participated in the focus groups	<b>9</b>
<b>TABLE 2</b> Characteristics of focus group participants	<b>11</b>
<b>TABLE 3</b> Contingency Management incentive schedule	<b>16</b>
<b>TABLE 4</b> Trial outcome measures, timing of administration and duration of participant completed questionnaires	<b>19</b>
<b>TABLE 5</b> Compliance according to group allocation vs. treatment received	<b>21</b>
<b>TABLE 6</b> Trial protocol amendment history	<b>24</b>
<b>TABLE 7</b> Baseline demographics by allocated group	<b>28</b>
<b>TABLE 8</b> Baseline outcomes by allocated group	<b>29</b>
<b>TABLE 9</b> Outcomes by allocated group at 6 and 12 months	<b>30</b>
<b>TABLE 10</b> Mean (SD), median and distribution for per cent adherence at month 6 by allocated group	<b>31</b>
<b>TABLE 11</b> Analysis by treatment allocated (ATA) analysis indicating odds ratio, marginal effects (95% CI) of % adherence at month 6 by allocated group derived from a fractional regression	<b>31</b>
<b>TABLE 12</b> Sensitivity analysis of differences in marginal means of per cent adherence to acamprosate at month 6 and 95% CI for key comparisons	<b>32</b>
<b>TABLE 13</b> Analysis by treatment allocated and CACE analysis by allocated group (per cent adherent to acamprosate at month 6)	<b>33</b>
<b>TABLE 14</b> Mean (SD), median and distribution for per cent days abstinent at month 6 by allocated group	<b>34</b>
<b>TABLE 15</b> Analysis by treatment allocated and CACE analysis by allocated group (per cent days abstinent at month 6)	<b>34</b>
<b>TABLE 16</b> Unit costs of health and social care services	<b>39</b>
<b>TABLE 17</b> Service use between baseline and the 6-month follow-up (complete case)	<b>42</b>
<b>TABLE 18</b> Disaggregated mean costs (£) (complete case)	<b>45</b>
<b>TABLE 19</b> Differences in imputed and adjusted costs	<b>46</b>
<b>TABLE 20</b> Differences in imputed and adjusted QALYs	<b>46</b>
<b>TABLE 21</b> Imputed and adjusted incremental medication adherence at 6 months	<b>51</b>

<b>TABLE 22</b>	Sensitivity analyses	<b>53</b>
<b>TABLE 23</b>	Outcomes by allocated group at 2 and 4 months	<b>83</b>
<b>TABLE 24</b>	Baseline and month 6 outcomes for those followed up within frame, and those not	<b>83</b>
<b>TABLE 25</b>	Prognostic analysis of predictors of medication adherence at month 6	<b>87</b>
<b>TABLE 26</b>	Prognostic analysis of predictors of PDA at month 6	<b>88</b>

# List of figures

<b>FIGURE 1</b> Alcohol Dependence and Adherence to Medicine trial CONSORT diagram	27
<b>FIGURE 2</b> Median and IQR for per cent days abstinent at month 6 by tercile of adherence to acamprosate for all participants and those still drinking at month 6	34
<b>FIGURE 3</b> Mean EQ-5D-5L health state scores over time by group	46
<b>FIGURE 4</b> Scatterplot showing the bootstrapped mean differences in imputed costs and imputed QALYs for SS + MM + CM compared to SS at 6 months	47
<b>FIGURE 5</b> Scatterplot showing the bootstrapped mean differences in imputed costs and imputed QALYs for SS + MM compared to SS at 6 months	47
<b>FIGURE 6</b> Cost-effectiveness acceptability curve showing the probability that SS + MM + CM is cost-effective compared to SS alone in terms of QALYs at 6 months	48
<b>FIGURE 7</b> Cost-effectiveness acceptability curve showing the probability that SS + MM is cost-effective compared to SS alone in terms of QALYs at 6 months	48
<b>FIGURE 8</b> Scatterplot showing the bootstrapped mean differences in imputed costs and imputed QALYs for SS + MM + CM compared to SS at 12 months	49
<b>FIGURE 9</b> Scatterplot showing the bootstrapped mean differences in imputed costs and imputed QALYs of SS + MM compared to SS at 12 months	49
<b>FIGURE 10</b> Cost-effectiveness acceptability curve showing the probability that SS + MM + CM is cost-effective compared to SS alone in terms of QALYs at 12 months	50
<b>FIGURE 11</b> Cost-effectiveness acceptability curve showing the probability that SS + MM is cost-effective compared to SS alone in terms of QALYs at 12 months	50
<b>FIGURE 12</b> Scatterplot showing the bootstrapped mean differences in imputed costs and imputed medication adherence for SS + MM + CM compared to SS at 6 months	51
<b>FIGURE 13</b> Scatterplot showing the bootstrapped mean differences in imputed costs and imputed medication adherence for SS + MM compared to SS at 6 months	52
<b>FIGURE 14</b> Cost-effectiveness acceptability curve showing probability that SS + MM + CM is cost-effective compared to SS in terms of acamprosate adherence at 6 months	52
<b>FIGURE 15</b> Cost-effectiveness acceptability curve showing the probability that SS + MM is cost-effective compared to SS in terms of acamprosate adherence at 6 months	53
<b>FIGURE 16</b> Scatterplot showing the bootstrapped mean differences in imputed costs and imputed QALYs for SS + MM + CM compared to SS modelled over 20 years	54

<b>FIGURE 17</b> Scatterplot showing the bootstrapped mean differences in imputed costs and imputed QALYs for SS + MM compared to SS modelled over 20 years	<b>54</b>
<b>FIGURE 18</b> Cost-effectiveness acceptability curve showing the probability that SS + MM + CM is cost-effective compared to SS in terms of QALYs modelled over 20 years	<b>55</b>
<b>FIGURE 19</b> Cost-effectiveness acceptability curve showing the probability that SS + MM is cost-effective compared to SS in terms of QALYs modelled over 20 years	<b>55</b>
<b>FIGURE 20</b> Distribution of primary outcome, per cent adherence to acamprosate at month 6	<b>84</b>
<b>FIGURE 21</b> SS + MM + CM vs. SS comparison of observed and imputed odds ratio and 95% CI for per cent days adherence at month 6	<b>84</b>
<b>FIGURE 22</b> SS + MM vs. SS comparison of observed and imputed odds ratio and 95% CI for per cent days adherence at month 6	<b>85</b>
<b>FIGURE 23</b> SS + MM + CM vs. SS + MM comparison of observed and imputed odds ratio and 95% CI for per cent days adherence at month 6	<b>85</b>
<b>FIGURE 24</b> SS + MM + CM vs. SS sensitivity analysis of missing data modelled by varying delta between -0.5 and 0	<b>86</b>
<b>FIGURE 25</b> SS + MM vs. SS sensitivity analysis of missing data modelled by varying delta between -0.5 and 0	<b>86</b>
<b>FIGURE 26</b> SS + MM + CM vs. SS + MM sensitivity analysis of missing data modelled by varying delta between -0.5 and 0	<b>86</b>

# List of abbreviations

ADAM	Alcohol Dependence and Adherence to Medicine	HLP	Healthy Living Pharmacy
AD-SUS	Adult Service Use Schedule	MAR	missing at random
APQ	Alcohol Problems Questionnaire	MEMS	Medication Event Monitoring System
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test-Lite	MM	Medication Management
		MMAS-8	Morisky Medication Adherence Scale
ATA	analysis by treatment allocated	MNAR	missing not at random
		NICE	National Institute for Health and Care Excellence
AUQ	Alcohol Urge Questionnaire	QALY	quality-adjusted life-years
BMQ	Beliefs About Medications Questionnaire	RCT	randomised controlled trial
		SADQ	Severity of Alcohol Dependence Questionnaire
CACE	complier average causal effect	SS	Standard Support
CEAC	cost-effectiveness acceptability curve	STAR	Scale to Assess Therapeutic Relationship
CM	Contingency Management	SURG	Service User Research Group
EQ-5D-5L	EuroQol-5 Dimensions, five-level version	TLFB	Time-Line Follow-Back



# Plain language summary

## What is the problem?

Many people who are trying to stop drinking alcohol can find it difficult to remain alcohol free. There is a medication called acamprosate (Campral) that can reduce cravings thereby increasing the likelihood of abstinence. However, some people have trouble taking the right amount of acamprosate tablets needed every day at the right time, preferably at mealtimes. This means the medication is not as effective. We have tested some new ways to help support people taking acamprosate.

## What did we do?

We tested three different strategies to find the best way to support people taking acamprosate. We recruited 739 people aged 18 and over who were receiving alcohol treatment to stop drinking and were taking acamprosate. We randomly allocated these people to three groups. The first was Standard Support, the usual support people receive when taking acamprosate. The second group received Standard Support plus Medication Management. This consisted of 12 telephone calls over 6 months with a trained pharmacist to discuss the importance of taking the right amount of the medication, how the medication works and strategies to help people take the medication correctly. The third group received Standard Support, Medication Management and Contingency Management. This involved giving people shopping vouchers for participating with Medication Management calls. The maximum value of vouchers per person was £120.

## What did we find out?

People who were in the group receiving Medication Management and Contingency Management took a greater number of acamprosate tablets. We also found that Medication Management plus Contingency Management was more cost-effective; there were greater gains in health with a smaller cost per person compared to Standard Support alone. This shows that there is likely to be a benefit to patients of Medication Management plus Contingency Management for supporting people taking acamprosate.



# Scientific summary

## Background

Alcohol is a significant risk factor for morbidity and mortality. In the UK there has been an increase in harm related to alcohol while also a reduction in funding to public health budgets, including alcohol services. While some individuals do successfully complete alcohol treatment, the majority will undergo frequent episodes of relapse. Providing effective treatment can reduce relapse rates and associated harms thus having a positive impact on cost-effectiveness.

The National Institute for Health and Care Excellence (NICE) recommends acamprosate in combination with psychological intervention as a first-line treatment for relapse prevention in alcohol dependence, however, acamprosate adherence poses a problem for its effectiveness in clinical practice. The reasons for non-adherence are complex and often due to multiple influences. Currently there is insufficient evidence as to which forms of intervention are effective in increasing adherence. Psychosocial interventions to support medication adherence have the potential to promote positive beliefs about medication and any concerns. Medication Management (MM) is a psychosocial intervention which aims to improve medication and treatment adherence by providing education, support, and practical advice about drinking behaviour and medication. There has also been an increasing focus on extending the role of the community pharmacist and the delivery of MM to improve medication adherence compliments this expanding role. Engagement in psychological interventions and retention in treatment is often poor in alcohol dependence but there is evidence that Contingency Management (CM) improves engagement and retention in substance use disorder treatment. There is currently limited evidence of its effectiveness within alcohol treatment but if shown to be effective it has the potential to also be adopted within the NHS and community pharmacies.

## Objectives

Our aim was to evaluate the effectiveness and cost-effectiveness of adjunctive MM with and without CM in improving adherence to acamprosate for relapse prevention in alcohol dependence.

1. To conduct a definitive three-arm, randomised controlled trial (RCT) of the effectiveness of MM with and without CM compared to Standard Support (SS) alone in enhancing adherence to acamprosate in alcohol dependence relapse prevention.
2. 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.
3. To assess the impact of adherence to acamprosate for alcohol dependence relapse prevention on abstinence and reduced alcohol consumption.

## Methods

### *Trial design*

This was a three-arm, parallel-group, pragmatic RCT, which began with an internal pilot phase to demonstrate recruitment, randomisation and interventions could be implemented as planned.

### *Eligibility and recruitment*

Participants presenting to alcohol services in one of the trial sites (London, Southampton, Birmingham, Yorkshire and Humber) who met the trial inclusion criteria were recruited via service staff.

### Participants

Inclusion criteria were: (1) adults, aged 18 years and over; (2) an *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision, diagnosis of alcohol dependence; (3) abstinent from alcohol at baseline assessment; (4) in receipt of a prescription of acamprosate; and (5) willing and able to provide informed consent. Exclusion criteria were: (1) a diagnosis of a severe physical/mental illness likely to preclude active participation in treatment or follow-up, (2) unable to understand verbal English at a level necessary to engage in the intervention and follow-up and (3) concurrent dependence on an illicit substance (other than cannabis).

### Randomisation and interventions

Participants were randomised in a 2 : 1 : 1 ratio to SS, SS + MM or SS + MM + CM using a stratified random permuted block method using a remote system. Participants and researchers were not blind to treatment allocation. SS typically comprised of monthly dispensing of prescribed acamprosate, monthly monitoring of the service user for 3 months by the specialist alcohol service, and then returned to the care of their GP for monthly monitoring in accordance with NICE guidelines and current clinical NHS clinical practice.

SS + MM participants followed the same care pathway as those in SS, with the addition of MM delivered by a central telephone support service by trained pharmacists. MM was delivered once a week for the first 6 weeks, reducing to once a fortnight for the following 6 weeks, and then monthly for 3 months.

SS + MM + CM participants followed the same care pathway as those in the SS + MM arm but with the addition of CM. Incentives in the form of vouchers were provided to reinforce attendance at MM sessions, up to a total of £120.

### Outcomes

The primary outcome measure was the self-reported per cent of medication taken as prescribed during the 6-month target phase of prescribing, post randomisation.

### Data collection

Data were collected at baseline, 2, 4, 6 and 12 months. Following an amendment, the 12-month follow-up was removed to maximise participant recruitment, and the recruitment period was extended without extending the trial end date. Data that had been collected at the 12-month follow-up were still included in the trial analysis plan. The primary outcome was collected at the 6-month follow-up.

### Sample size

The sample size aimed to detect a clinically important effect size difference of 0.3, about 13% difference in per cent adherence. In order to make the study cost-efficient, we proposed to allocate twice as many to the SS group than to the SS + MM and SS + MM + CM groups. With power at 80%, alpha of 0.05 and a two-sided test, this required 524 to be followed up at the primary end point, 262 in the SS group and 131 in each of the other groups. We anticipated a loss to follow-up at month 6 of 30% and inflated the required sample at baseline to 748 to account for this. Sample sizes were calculated using Stata 12 (StataCorp LP, College Station, TX, USA).

### Statistical methods

The primary analysis was an analysis by treatment allocated (ATA) and was based on all available data for participants who were randomised, irrespective of whether they complied with their allocation or not.

The primary analysis was based on the ATA. Secondary analyses examined treatment effects under different scenarios for compliance with allocation/treatment: complier average causal effects (CACE). Two scenarios of compliance were defined in this trial. The first compliance for those in the SS + MM and SS + MM + CM group was defined as adhering to at least 50% of the MM calls. In the second, the

threshold was increased to 100%. Both scenarios are modelled in the analysis. We considered missing data as being missing at random (MAR) or missing not at random (MNAR). We conducted a multiple imputation to address MAR and a sensitivity analysis to address MNAR.

Fractional regression was conducted to model the relationship between pre-randomisation factors and per cent adherence to acamprosate and per cent days abstinent from alcohol at month 6. Interaction terms with treatment allocation were included in the model and a significance level of 0.1 was used as a threshold to determine which variables were maintained in the final model reported. Baseline variables included initially in the model include age, gender, marital status, ethnicity, employment status, number of children, age of first drink, weekly and daily drinking, frequency and quantity of alcohol consumption, severity of alcohol dependence, alcohol urges and alcohol-related problems. This analysis was augmented with an additional analysis for the SS + MM and SS + MM + CM groups where the same dependent variable was assessed with the same independent variables with the addition of therapeutic alliance.

## Method of economic evaluation

The primary economic analysis was a cost-utility analysis where outcomes were expressed as quality-adjusted life-years (QALYs), as recommended by NICE. A secondary analysis explored cost-effectiveness in terms of the primary clinical outcome which was adherence to relapse prevention medication. The primary economic perspective was the NHS and personal social services (NHS/PSS) perspective preferred by NICE.

The primary time horizon of the economic analyses using both QALYs and relapse medication adherence was the 6-month follow-up, consistent with the primary clinical analysis. A secondary analysis was carried out at the 12-month follow-up using QALYs. The primary economic outcome was QALYs calculated using the EuroQol-5 Dimensions, a five-level version measure of health-related quality-of-life scores at baseline, 6- and 12-month follow-ups.

The primary economic analysis was composed of two separate comparisons: (1) SS + MM + CM versus SS alone; and (2) SS + MM versus SS alone, both at 6 months post randomisation, and assessed cost-effectiveness in terms of cost per QALY using the EuroQol-5 Dimensions measure of quality of life. Two secondary economic evaluations were carried out, a cost-utility analysis at 12 months post randomisation and a cost-effectiveness analysis using adherence to relapse medication which was the primary clinical outcome. Cost-effectiveness was explored using incremental cost-effectiveness ratios (difference in mean cost divided by difference in mean effect) and cost-effectiveness acceptability curves (CEACs), which show the probability that SS + MM + CM or SS + MM are cost-effective compared to SS alone for different levels of willingness to pay for improvements in outcome.

Sensitivity analyses were carried out to test the impact of varying methods and assumptions on the relative cost-effectiveness of the interventions being compared. We planned three sensitivity analyses: (1) a broader analytical perspective to include the cost of crime (which was not completed as no crimes were reported), (2) a complete case analysis for comparison with the results that used multiple imputation for missing data and (3) a cost-utility analysis using QALYs calculated from EuroQol-5 Dimensions, three-level version tariffs.

## Results

A total of 1459 potential participants were approached of whom 1019 (70%) were assessed. Of these 739 (73%) were eligible and consented to participate in the study. Allocation was in the ratio of 2 : 1 : 1, 372 (50%) were allocated to SS, 182 (25%) to SS + MM and 185 (25%) to SS + MM + CM. At the primary end point, 6 months post randomisation, 518 (70%) were successfully followed up with 255 (68.5%)

allocated to SS, 122 (67.0%) to SS + MM and 141 (76.2%) to SS + MM + CM. There were no serious adverse events related to the trial interventions reported.

The mean difference in per cent adherence to acamprosate at month 6 between those allocated to SS and SS + MM + CM versus SS was 10.6% [95% confidence interval (CI) 19.6% to 1.6%]; this difference was statistically significant. When the SS + MM group was compared to SS alone, the SS + MM group had a lower per cent days adherent than the SS group, mean difference 3.1% (95% CI 12.8% to -6.5%); this was not significant. A similar non-significant finding was seen when we compared the SS + MM and SS + MM + CM groups, mean difference 7.9% (95% CI 18.7% to -2.8%).

Our secondary analysis included per cent days abstinent from alcohol at month 6. The ATA found differences favouring both intervention groups over SS alone but neither of these was significant. When a CACE analysis was conducted using scenario 2, both intervention groups had a significantly greater per cent days abstinent than SS alone. This analysis also highlighted the relationship between adherence to acamprosate and better outcomes, something additionally highlighted by a significant correlation between adherence to acamprosate and increased per cent days abstinent at month 6. CACE analysis: Under scenario 1, 50% adherence, the mean difference in per cent adherence increases from 10.6% (95% CI 19.6 to 1.62) to 12.4% (95% CI 17.8% to 7.1%) in the SS + MM + CM versus SS comparison, indicating that at 50% compliance those allocated to SS + MM + CM have a mean of 12.44% more adherence to acamprosate at month 6 than those allocated to SS alone. When comparing the SS + MM versus the SS group, a previous non-significant difference 3.14% (95% CI 12.8% to -6.5%) becomes a significant difference of 13.2% (25.4–1.15%). Under scenario 2, the differences are larger in magnitude, the SS + MM + CM group having 22.2% (95% CI 29.7% to 14.7%) more adherent days than the SS group alone. At the same time, the magnitude of difference is larger for the SS + MM versus SS comparison 31.8% (95–60.5% vs. 3.10%), although this comparison is based on a small number of participants, 20, and should be interpreted with caution.

For SS + MM + CM versus SS, the primary economic analysis at 6-month follow-up using QALYs, the secondary economic analysis at 6-month follow-up using medication adherence and the economic modelling over a 20-year time horizon using QALYs all found SS + MM + CM to dominate SS (better outcomes at lower cost). At 12-month follow-up, although SS + MM + CM was not dominant, it generated more QALYs at an additional cost that was below the NICE cost per QALY threshold. CEACs also showed there was a higher probability of SS + MM + CM being cost-effective compared to SS alone in all analyses and at all time points.

For SS + MM versus SS, at 6- and 12-month follow-up and when modelled over 20 years, SS + MM achieved better outcomes at higher cost compared to SS. In terms of cost-effectiveness, SS + MM was not found to be cost-effective at 6-month follow-up but had a higher probability of being cost-effective compared to SS at both the 12-month follow-up (using the higher £30,000 per QALY NICE threshold) and when modelled over 20 years (over the full £20,000–30,000 cost per QALY threshold).

## Conclusions

When comparing SS + MM + CM versus SS alone, we observed a significantly higher per cent adherence to acamprosate in the SS + MM + CM group, and the differences were of the magnitude that would indicate a clinically important difference. Differences were also observed when comparing SS + MM versus SS and SS + MM + CM versus SS + MM, but these were not significant. We explored how robust these findings were to assumptions about the nature of any missing data and we explored a missing data imputation model to explore the impact of data that may be MAR and a sensitivity analysis to explore data that may not be MAR. Neither of these analyses found any significant deviation from the analysis based on observed values, we can be confident that our findings from the ATA analysis are robust. To explore the effect of compliance to MM we conducted a CACE analysis using two scenarios of

compliance, 50% and 100%. In both scenarios, we found greater benefits associated with SS + MM + CM and SS + MM versus SS alone and these benefits were significant and clinically important.

There were several limitations to the current trial that should be taken into consideration. The trial's primary outcome measure changed substantially due to data collection difficulties and therefore relied on a measure of self-reported adherence. A lower than anticipated follow-up rate at 12 months may have lowered the statistical power to detect differences in the secondary analyses, although the primary analysis was not impacted.

The results of the primary economic analysis at the 6-month follow-up point suggest that MM was only cost-effective when supported by incentives to encourage support session uptake. This finding was heavily influenced by lower total costs in the SS + MM + CM group as a result of lower use of residential rehabilitation facilities compared to both SS + MM and SS alone, which may be related to the significantly higher medication adherence seen in the CM group. Over the medium (12 months) and longer term (20 years), SS + MM + CM remained cost-effective compared to SS and there was a higher probability of SS + MM being cost-effective compared to SS. These results support the addition of MM to SS for alcohol dependence, with or without CM. However, the economic benefit was stronger when CM was included.

## Trial registration

This trial is registered as ISRCTN17083622 <https://doi.org/10.1186/ISRCTN17083622>.

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# Chapter 1 Introduction

Material throughout the chapter has been adapted from the trial protocol.<sup>1</sup>

## Background and rationale

Alcohol is a significant risk factor for morbidity and mortality, and is causally related to over 200 non-communicable diseases and injuries.<sup>2,3</sup> The World Health Organization reports that 3 million deaths were caused by harmful alcohol use worldwide in 2018.<sup>4</sup> In the UK, there has been a consistent, year-on-year increase in harm related to alcohol. There were almost 1.3 million NHS hospital admissions related to alcohol in 2018–19, an 8% increase from the previous year.<sup>2</sup> Chronic physical health conditions related to alcohol use have increased in prevalence in the UK, including certain cancers, neuropsychiatric conditions, cardiovascular and digestive diseases, alcoholic liver disease and alcohol use disorders.<sup>5,6</sup> Chronic, heavy alcohol use is also associated with an increased risk of mental health disorders<sup>7</sup> and contributes to social problems such as unemployment, poor quality of life, marital breakdown and domestic violence.<sup>8–11</sup> The cost to the UK economy due to the physical, mental and social problems associated with alcohol is estimated at £21B annually, of which the NHS costs are estimated at £3.5B.<sup>3,12</sup>

In the UK, the proportion of adults drinking more than the recommended unit guidelines (14 units a week) varied between age groups, with men and women aged 55–64 years being the most common (38% and 19%, respectively).<sup>2</sup> Across all age groups, men were more likely than women to drink at increasing and higher risk levels.<sup>2</sup> The number of adults entering specialist alcohol treatment has fallen since a peak in 2013–14, decreasing each year until present day 2019–20.<sup>13</sup> In this same period, there have been substantial cuts to public health budgets, including alcohol services.<sup>14,15</sup> Frequent episodes of relapse and resumption of drinking are common in those dependent on alcohol, as many as 70% of service users relapse in the first 12 months post treatment.<sup>16,17</sup> Reducing alcohol-related hospital admissions and NHS costs has been identified as a priority in the UK Government's Alcohol Strategy.<sup>3</sup> The combined benefits of drug and alcohol treatment amount to £2.4B every year, resulting in savings from areas including crime and health and social care. Alcohol treatment has been shown to reflect a return on investment of £3 for every £1 invested.<sup>18–20</sup> Providing effective treatment for alcohol dependence to reduce relapse rates, and therefore alcohol-associated harms, will help to achieve this.

### *Acamprosate for relapse prevention in alcohol dependence*

Acamprosate and naltrexone have been recommended by the National Institute for Health and Care Excellence (NICE), in combination with a psychological intervention, as first-line treatments to support relapse prevention in alcohol dependence.<sup>21</sup> Disulfiram is regarded by NICE as a second-line treatment due to a more limited evidence base and potential adverse effects. In the past 10 years, there has been a 58% increase in prescriptions for these medications issued, however, in the past 3 years, there has been a slight decrease.<sup>2</sup> Naltrexone has been licensed for use in the UK to support relapse prevention in alcohol dependence since May 2013 and can also be used to treat opioid dependence. As the reason for prescription is not recorded in the NHS prescription service, the prescribing data for this in relation to alcohol dependence cannot be directly compared against acamprosate.<sup>2</sup> However, Prescription Cost Analysis data produced by the NHS Business Service Authority for 2012 shows that there were 117,417 acamprosate prescription items compared to just 17,790 prescription items for naltrexone.<sup>13,22</sup> Since naltrexone has been granted marketing authorisation for alcohol dependence, this difference seems not to have changed.<sup>23</sup> As these data include prescriptions for naltrexone to treat opiate dependence, the number of prescription items for alcohol dependence is likely to be fewer than indicated. Due to this difference in prescribing practices and differences in dosing regimens and side effects between medications, which may affect adherence, acamprosate was the focus for the current research.

Acamprosate modulates the glutamatergic system and attenuates the imbalance between inhibitory (GABA) and excitatory (glutamate) neurotransmitters in the brain during alcohol withdrawal, reducing the conditioned effect of alcohol and the negative reinforcement of the addictive behaviour.<sup>24-27</sup> A meta-analysis found acamprosate to have a moderate effect on maintenance of abstinence in people with alcohol dependence.<sup>26</sup> These results have been supported by a more recent systematic review and meta-analysis that found acamprosate to be the only alcohol relapse prevention intervention with enough evidence to conclude that it is better than placebo in supporting detoxification and for alcohol-dependent patients to maintain abstinence for up to 12 months in primary care settings. There was additional evidence that acamprosate might be effective longer term but the evidence was weak.<sup>28</sup>

### ***Adherence to acamprosate***

Poor adherence to medication is a common problem, particularly in chronic conditions, a greater risk of poor adherence has also been associated with substance use disorder.<sup>29,30</sup> Although the available evidence supports the efficacy of acamprosate in clinical trials, poor adherence to the medication may pose a problem for effectiveness in clinical practice. We conducted a systematic review of the rates of adherence to acamprosate reported in clinical trials. We found that the mean adherence rate reported ranged from 54.2%<sup>31</sup> to 95%.<sup>32</sup> This variation in adherence may be partially explained by differences in the definition of medication adherence (e.g. percentage of prescribed medication taken or percentage of those taking 80% or more of prescribed medication) and measurement of adherence. Several different methods are used in clinical trials to monitor medication adherence, with variation in the confidence in their accuracy. For example, counting returned medication and self-report of adherence may be considered 'low' confidence measures, electronic monitoring of pill bottle opening 'medium confidence' and supervised dosing 'high confidence'.<sup>33</sup> Medication non-adherence in clinical practice is likely to be significantly greater than that seen in clinical trials that often offer payment for participation, adherence support and frequent monitoring appointments.

The median duration of acamprosate pharmacotherapy has been found to be only 2.1 months with just 27.7% of those prescribed acamprosate persisting for 6 months as recommended by NICE.<sup>34</sup> Therefore, patients may not be gaining the maximum benefits from the medication.<sup>21</sup> Medication effectiveness can be further limited by underdosing, overdosing or taking medication at incorrect intervals.<sup>35</sup> The Testing Combined Pharmacotherapies and Behavioral Interventions in Alcohol Dependence trial, a large US-based trial, found an association between poor adherence to both acamprosate and naltrexone and lower percentage days abstinent and higher percentage days heavy drinking.<sup>36,37</sup> Furthermore, poorer alcohol outcomes were also identified in those who were non-adherent early in the Testing Combined Pharmacotherapies and Behavioral Interventions in Alcohol Dependence trial compared to those who were non-adherent later in the trial.<sup>36,37</sup>

### ***Reasons for non-adherence***

Poor adherence to a medication may be due to multiple and complex reasons.<sup>29</sup> The complexity of the dose regimen, with greater dose frequency and complexity of instructions, has been associated with poorer adherence.<sup>38-40</sup> Side effects were commonly reported as impacting on adherence in the Testing Combined Pharmacotherapies and Behavioral Interventions in Alcohol Dependence trial.<sup>36,37</sup> Poorer adherence was also found for the trials combined therapy group compared to the single active therapy group, which may be explained by an increase in side effects experienced by participants taking both acamprosate and naltrexone.<sup>30</sup>

Horne has proposed that patients weigh up the potential costs and benefits of medication when making adherence decisions.<sup>41,42</sup> Greater adherence to medications in chronic health conditions such as asthma, diabetes, cardiac disease and cancer has been associated with a greater perception of the benefits of the medication. Conversely, greater concern about potential side effects of medication has been associated with poorer adherence.<sup>42,43</sup> The development of effective interventions to address the uncertainty that some patients feel towards the benefits of medication and their concerns about the potential adverse effects is a priority to improve adherence in the treatment of chronic health conditions.<sup>35,43</sup>

## Medication Management

The NICE alcohol treatment guidelines<sup>21</sup> recommend monthly supervision for the first 6 months while taking acamprosate. There is a wide variation in the type and frequency of support received in clinical practice with support usually delivered by a combination of primary care and specialist addiction services.

Psychosocial interventions to maximise adherence to medications for alcohol relapse prevention, including acamprosate, have been used successfully in clinical trials. A six-stage, manualised intervention called BRENDA (Biopsychosocial evaluation, Report, Empathy, Needs assessment/goals, Direct advice, and Assessment)<sup>44</sup> has been found to be beneficial for improving adherence to medication for alcohol relapse prevention.<sup>45,46</sup>

The manual-based psychosocial intervention, Medical Management, was developed from BRENDA and other Medication Management (MM) interventions<sup>47</sup> for the Testing Combined Pharmacotherapies and Behavioral Interventions in Alcohol Dependence trial<sup>48</sup> and it has since been used in clinical trials of other medications.<sup>49,50</sup> Medical Management provides education, support and practical advice to service users about their alcohol drinking behaviour and medication to support adherence. An initial session, lasting up to 60 minutes, identifies the rationale for taking the prescribed medication, provides an overview of the dosing regimen, highlights the importance of taking the medication as it has been prescribed and an individualised plan to support adherence is developed. In addition, the service users' diagnosis, treatment goals and participation in support groups are discussed. The initial session acts as a foundation for the preceding shorter Medical Management sessions that last up to 30 minutes. Despite the successful inclusion of the MM interventions BRENDA and Medical Management in clinical trials, research to support their use in clinical practice is lacking.

## The role of the pharmacist

The community pharmacist's role has extended beyond medication supply to improve public health,<sup>51–55</sup> HIV prevention in opioid dependence<sup>56–58</sup> and supporting adherence to medication.<sup>59–61</sup> A joint statement by the Royal College of General Practitioners and the Royal Pharmaceutical Society in 2011 identified a role for suitably qualified community pharmacists to contribute to care planning and treatment interventions in substance use disorder (RCGP and RPS, 2011). This has been followed by a recent report of the commission on the future models of NHS care delivered through pharmacy.<sup>62</sup>

Healthy Living Pharmacies (HLPs) aim to provide a range of health promotion interventions, with alcohol dependence as one of the conditions targeted.<sup>55,63,64</sup> Community pharmacists and support staff have expressed positive attitudes towards providing extended services in alcohol and substance use disorder when adequate training is provided.<sup>65–67</sup>

## Contingency Management

Engagement and retention in treatment for alcohol dependence are often suboptimal and are related to poor treatment outcomes.<sup>68,69</sup> Contingency Management (CM) has been found to improve substance use disorder treatment retention and engagement<sup>70–74</sup> as well as increase adherence to prescribed pharmacotherapies such as naltrexone for opiate relapse prevention<sup>75</sup> and improve prevention, diagnosis and treatment outcomes for HIV, tuberculosis and hepatitis control in substance use disorders.<sup>76</sup> There is also evidence of an increased rate of abstinence of cannabis use over and above evidenced-based treatment (individual Motivational Enhancement Therapy/Cognitive Behavioural Therapy),<sup>77</sup> reduced tobacco and alcohol use among adults not in treatment for substance use disorders,<sup>78</sup> and it is effective for cocaine, tobacco, opiates and cocaine, and polysubstance use.<sup>79,80</sup>

Research on the use of CM in the treatment of alcohol dependence is limited.<sup>21,80</sup> A systematic review<sup>81</sup> concluded that CM continues to be a highly effective intervention for a range of substance use disorder treatment and follow-up outcomes, showing sustained growth and high treatment efficacy, and recommends further dissemination and implementation of CM to increase its impact.

Petry *et al.*<sup>82</sup> examined the use of CM and the common concerns of its implementation and recommend that more research needs to be done to promote a better understanding of CM and its benefits. It is this lack of understanding that leads to CM being underutilised despite its clearly effective results in substance use disorder treatment outcomes. Subsequently, a systematic review of the dissemination and implementation of CM has been conducted.<sup>83</sup> The findings report the importance of organisational input and ongoing supervision and consultation to optimise the effects of CM as well as including barriers to implementing CM, the main one being cost despite evidence of CM's cost-effectiveness.<sup>84</sup>

Studies can use a prize-based protocol with incentives of variable magnitude based on abstinence and/or treatment participation.<sup>85,86</sup> Alternatively, fixed monetary incentives or monetary incentives on an escalating scale may also be used, for example, to improve substance use disorder treatment retention and drug use and post-traumatic stress disorder outcomes,<sup>87</sup> improve retention and abstinence with stimulant users in outpatient psychosocial treatment programs,<sup>88</sup> improve hepatitis B vaccination adherence and completion in injecting drug users and to reduce heavy alcohol consumption.<sup>89</sup>

### **Why this research is needed now**

The effectiveness of acamprosate to support alcohol relapse prevention has been well documented.<sup>21,26,28,46,48</sup> The full benefit of acamprosate in clinical practice has not been maximised due to poor adherence and insufficient duration of its use. Supporting patients in taking acamprosate as prescribed through the application of MM has the potential to help improve adherence and increase the clinical effectiveness of acamprosate. However, there is currently insufficient evidence to determine the most effective form of intervention to support adherence.

The delivery of MM within the pharmacy setting is aligned with the development and expansion of the role of the pharmacist.<sup>55,62–66,90,91</sup> However, the effectiveness of interventions to increase medication adherence for alcohol dependence delivered by pharmacists is currently not known.

Research into the application of CM in alcohol dependence treatment has been recommended by NICE<sup>21</sup> to build on the existing small, but growing, body of evidence.<sup>70,78,92</sup> The financial cost of delivering CM is low (<£10 per session) and extensive training to deliver the intervention is not required. If shown to be effective, CM has considerable potential to be adopted within NHS services and community pharmacy to enhance alcohol dependence treatment.

## **Aims and objectives**

The current trial, ADAM (Alcohol Dependence and Adherence to Medicine), aimed to evaluate the effectiveness and cost-effectiveness of adjunctive MM with and without CM in improving adherence to acamprosate for relapse prevention in alcohol dependence.

### **Objectives**

- To conduct a definitive three-arm, randomised controlled trial (RCT) of the effectiveness of MM with and without CM compared to Standard Support (SS) alone in enhancing adherence to acamprosate in alcohol dependence relapse prevention.
- 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.
- To assess the impact of adherence to acamprosate for alcohol dependence relapse prevention on abstinence and reduced alcohol consumption.

### Primary hypothesis

The primary null hypothesis was:

- MM and MM + CM will be no more effective than SS alone in terms of per cent adherence to acamprosate, 6 months post randomisation.

### Secondary hypotheses

The secondary null hypotheses were:

- MM and MM + CM will be no more cost-effective than SS alone at 6 months post randomisation.
- MM and MM + CM will be no more effective than SS in terms of the percentage of possible doses of acamprosate taken, at 12 months post randomisation.
- MM and MM + CM will be no more cost-effective than SS alone in terms of quality-adjusted life-years (QALYs) at 12 months post randomisation.
- No greater adherence to acamprosate will be associated with improved alcohol outcomes, namely a higher percentage of days abstinent, fewer units of alcohol per drinking day, 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 not be moderated by medication adherence at 6 and 12 months post randomisation.



## Chapter 2 Intervention development and pharmacist training

A manualised version of MM has been designed for use in clinical trials<sup>48,93</sup> and a shortened version of this manual has been produced for use in routine clinical practice.<sup>94</sup> However, the content and structure of the manual required some adaptation for use with UK community pharmacists. CM has been extensively used to enhance treatment engagement and medication adherence in substance use disorder, and to a lesser extent in alcohol dependence. Adaptation of the CM procedures was also required for the UK community pharmacy setting to support attendance at MM sessions. We aimed to adapt the standardised MM manual and develop a suitable CM protocol to be delivered by trained pharmacists to improve adherence to acamprosate for alcohol relapse prevention.

This chapter contains four elements supporting the development of MM and CM interventions and pharmacist training:

1. focus groups with service users and pharmacists
2. patient and public involvement
3. manual development and adaptation (based on 1–2)
4. pharmacist training.

### Focus groups with service users and pharmacists

To support this aim, we conducted focus groups with service users and pharmacists/pharmacy support staff to explore the following:

1. service users' past experiences of taking acamprosate, the support received while taking the medication and any perceived benefits and concerns about acamprosate
2. service users' views on factors influencing medication adherence and specifically adherence to acamprosate
3. service users' views on MM and its delivery in the pharmacy setting/being pharmacist delivered
4. service users' views on the optimal incentive schedule for CM to improve attendance at MM sessions
5. pharmacist/pharmacy support staff beliefs, attitudes and knowledge of alcohol dependence
6. pharmacists/pharmacy support staff perceptions of factors that may influence adherence to acamprosate
7. pharmacist/pharmacy support staff views on the barriers and facilitators to delivering MM and CM within the pharmacy setting
8. pharmacist/pharmacy support staff previous experiences of delivering health interventions, their self-perceived training needs, and the support that they would like/feel that they need to deliver MM and CM in relation to alcohol dependence

### Methods

The full methods and results have been published elsewhere.<sup>95</sup>

The study received local NHS approvals, and NHS research ethics approval from the West of Scotland Research Ethics Committee (Ref: 15/WS/0048).

### Setting

Eight focus groups were conducted, four with service users with experience in treatment for alcohol dependence and four with pharmacists/pharmacy support staff. Focus groups took place in four

different geographical locations (London, Birmingham, Southampton, Hull) in line with the study sites of the main ADAM trial, so that any issues relating to geographical location and differences in treatment practices could be considered. Focus groups were used to allow a range and depth of ideas to be explored among individuals with a shared experience.<sup>96,97</sup>

## Participants

There is no optimum number of participants for a focus group but it has been suggested that between six and ten participants enable a discussion with varied perspectives.<sup>98</sup> Purposive sampling was used to identify up to 12 participants to invite to each focus group to achieve a recruitment rate of between 6 and 10 participants per focus group.<sup>99</sup> Service users were identified through service user involvement and recovery groups in each locality. Service users were included if they had received treatment for alcohol dependence. In an attempt to ensure that all participants felt comfortable expressing their views, we aimed for a 50/50 composition of those who had and those who had not had previous experience with acamprosate. Pharmacists/pharmacy support staff were identified through Pharmacy Area Managers for the pharmacy locations where the focus groups were taking place. Participants were recruited irrespective of age, gender and ethnicity. People unable to understand verbal explanations given in English were excluded given that focus groups rely on verbal interaction between participants to gain a rich data set. People who were unable to adequately understand verbal English were considered unlikely to be able to participate adequately in focus groups where ideas and topics of conversation could move at a fast pace. The use of an interpreter was also discounted on the grounds that it would interfere with the group dynamic.

## Procedure

All potential participants were given written information about the research and a minimum of 24 hours to consider their participation and ask any questions before providing written informed consent. The Participant Information Sheet highlighted participants' right to withdraw from the research at any time without giving reason (see Project Webpage Document for Participant Information Sheet and Consent Form). Focus groups were facilitated by a member of the research team (see Project Webpage Document for the topic guide). A second facilitator took notes on the session and gave a brief presentation at the start of the focus group to explain the purpose of the study and to describe the interventions of MM and CM. A visual summary of the ADAM study, an example of a CM schedule, and actual adherence recording bottles with the electronic Medication Event Monitoring System (MEMS) cap were shown to participants at the start of each focus group to aid their understanding. All groups lasted 60–90 minutes and were audio-recorded and transcribed in full. All participants were reimbursed their travel expenses and given £20 cash to thank them for their time. Data were anonymised and stored securely (password-protected computers/laptops, locked filing cabinets in lockable offices in buildings with swipe access and security presence) in accordance with Good Clinical Practice and King's College London's Standard Operating Procedures.

## Analysis

A modified framework analysis was used to analyse the data thematically.<sup>100,101</sup> Codes were developed inductively from the transcripts as well as deductively from the topic guide by a researcher allocated to analyse each focus group. The transcripts were coded line by line using NVivo (version 11) (QSR International, Warrington, UK) program.

## Results

### Service user focus groups

Please see [Table 1](#) for an overview of the participant characteristics.

Four themes were identified:

### 1. Concerns about support and availability of alcohol relapse prevention medication

Participants reported difficulties accessing relapse prevention treatment, including acamprosate, and limited professional support following alcohol withdrawal. Participants reported accessing alternative types of support, other than with health-care professionals including mutual aid groups (e.g. alcoholics anonymous and SMART groups).

### 2. Perceptions of acamprosate treatment

There were conflicting views on the benefit of acamprosate. Many participants expressed that acamprosate could help them reduce their cravings and remain abstinent for longer. However, others appeared to doubt the effectiveness of acamprosate. Participants from all groups expressed

**TABLE 1** Characteristics of the service users who participated in the focus groups [values are numbers (%) unless stated otherwise]

Characteristics	Focus group Site 1 (n = 10)	Focus group Site 2 (n = 6)	Focus group Site 3 (n = 5)	Focus group Site 4 (n = 5)	Total (n = 26) <sup>a</sup>
Age years: mean (SD), range	50 (7.91), 35–60 <sup>a</sup>	45 (2.80), 42–50	45 (9.26), 30–54	52 (12.17), 35–69	48 (8.36), 30–69 <sup>b</sup>
Gender					
Female	5 (50)	2 (33)	1 (20)	2 (40)	10 (38)
Male	5 (50)	4 (67)	4 (80)	3 (60)	16 (62)
Ethnicity					
Asian/Asian British	0 (0)	1 (17)	0 (0)	0 (0)	1 (4)
Black/African/Caribbean/Black British	2 (20)	0 (0)	0 (0)	0 (0)	2 (8)
Mixed/multiple ethnicity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
White British	7 (70)	4 (67)	5 (100)	5 (100)	21 (81)
White Irish	1 (10)	1 (17)	0 (0)	0 (0)	2 (7)
Currently receiving relapse prevention treatment (psychosocial or pharmaceutical) for alcohol dependence					
Yes	4 (40)	5 (85)	3 (60)	3 (60)	15 (58)
No	6 (60)	1 (17)	2 (40)	2 (40)	11 (42)
Ever been prescribed acamprosate					
Yes	2 (20)	5 (83)	4 (80)	2 (40)	13 (50) <sup>c</sup>
No	8 (80)	1 (17)	1 (20)	3 (60)	13 (50)

SD, standard deviation

<sup>a</sup> Site 1 (London), Site 2 (West Midlands), Site 3 (Wessex) and Site 4 (Yorkshire & Humber).

<sup>b</sup> Missing data for one participant.

<sup>c</sup> Of the total 13 participants who are prescribed acamprosate, six were prescribed during 2015, four in 2014, one in 2013, one in 2012 and one during 2003–4.

concerns about the side effects of acamprosate (e.g. gastrointestinal problems and nausea) and it appeared that participants were not made aware of the potential side effects and were unsure how to seek help if they were experienced. Participants from all groups expressed difficulties with taking acamprosate, particularly remembering to take six tablets a day. Few expressed that the number and frequency of tablets created an additional barrier as they were taking multiple medications for other health concerns.

### 3. Perceptions of acamprosate adherence telephone support role for pharmacists

Participants from all focus groups expressed positive views of pharmacists being able to help resolve their concerns of acamprosate. Participants agreed that intervention calls should be structured, take place regularly, have flexibility in the length of the call according to need, and be led by the service user. Participants also expressed a need for greater support during more difficult times in their recovery, in particular, the initial period following alcohol withdrawal. There was some concern expressed by participants in each of the focus groups that telephone support could be impersonal and face-to-face was preferred. Some participants expressed some uncertainty with how knowledgeable and skilled pharmacists would be to provide telephone support for acamprosate and they also highlighted the need for good communication skills for this role.

### 4. Perceptions of CM to support acamprosate adherence

Participants initially expressed strong negative views towards CM, expressing that individuals should not be rewarded for engaging in treatment. Participants had reservations related to the effectiveness of CM and held the belief that the money would be used to buy alcohol. However, during the focus group, initial negative views became more positive when considering CM in the context of rewarding someone in recovery. The type of CM incentive was discussed by participants and it was suggested that it should be practical and relevant to the needs of the service user. Furthermore, participants indicated a preference for the payment of the CM incentive to be given at intervals throughout the trial. Participants suggested alternatives to cash expressing that they wanted the incentives to not only impact them financially but also personally and make them feel valued.

## Pharmacist focus groups

Please see [Table 2](#) for an overview of the participant characteristics.

Five themes were identified:

### 1. Challenges affecting medication adherence

This theme refers to the barriers and incentives to patients' adherence to medications, including the importance of adherence to treatment effectiveness as well as ways to support adherence.

### 2. Assumptions about patients with alcohol problems

Participants in the focus groups expressed some assumptions made about those with alcohol dependence that related to their socioeconomic status, mistrust of health-care professionals, inevitability of relapse and comorbid problems. Pharmacists also expressed some negative attitudes and perceptions towards patients with alcohol problems. They separated the patient group as being 'other' or different to professionals, and implied that this patient group would be particularly motivated by money.

**TABLE 2** Characteristics of focus group participants [values are numbers (%) unless stated otherwise]

Characteristics	Focus group Site 1 (London) (n = 6)	Focus group Site 2 (West Midlands) (n = 5)	Focus group Site 3 (Wessex) (n = 4)	Focus group Site 4 (Yorkshire and The Humber) (n = 3)	Total (n = 18)
Age years: mean (SD), range	42 (11.68), 29–60 <sup>a</sup>	47 (11.28), 29–58	34 (5.26), 28–37 <sup>a</sup>	52 (9.71), 44–63	44 (11.21), 28–63
Gender					
Female	1 (17)	1 (20)	1 (25)	1 (33)	4 (22)
Male	5 (83)	4 (80)	3 (75)	2 (67)	14 (78)
Ethnicity					
Asian/Asian British	6 (100)	2 (40)	2 (50)	0 (0)	10 (56)
White British	0 (0)	3 (60)	2 (50)	3 (100)	8 (44)
Years registered as a pharmacist: mean (SD), range	20 (12.48), 2–36	25 (12.98), 4–37	11 (5.26), 5–15	30 (8.94), 21–39	21 (11.96), 2–39
Years practiced as a community pharmacist: mean (SD), range	20 (12.48), 2–36	25 (12.98), 4–37	11 (5.26), 5–15	30 (8.94), 21–35	20 (11.52), 2–37
Drug misuse training since registration (hours): mean (SD), range	25 (18.33), 29–60	218 (313.54), 0–750	14 (8.64), 4–23	29 (8.78), 20–38	77 (177.17), 0–750
Smoking cessation training since registration (hours): mean (SD), range	90 (115.02), 8–42	24 (17.10), 0–45	13 (14.59), 3–35	28 (20.46), 10–50	44 (71.97), 0–50
Alcohol misuse training since registration (hours): mean (SD), range	10 (10.71), 0–30	34 (39.27), 0–90	1 (0.96), 0–2	6 (8.14), 0–15	14 (24.14), 0–90

<sup>a</sup> Missing data for one participant.

### 3. Pharmacists' training and support needs

Pharmacists expressed concerns about the existing burden and work pressures they face, and highlighted challenges to combining their clinical work with research activities within a pharmacy setting. They expressed there was lack of alcohol-specific training as well as time to undertake the training.

### 4. Practical considerations on the delivery of an alcohol relapse medication adherence service

Pharmacists appeared inquisitive about the ADAM study and the proposed health intervention; this included querying the rationale to establish their understanding of how the study would work. They showed interest with the study and its proposed methods. Pharmacists had an overall positive view of research, deeming it to be worthwhile and something pharmacists would engage with.

### 5. Unique professional characteristics of pharmacists

The pharmacists expressed the uniqueness of their role as pharmacists in the community to provide health-care advice and services to their patients and the public. They highlighted the benefits of involving pharmacists in research and this was an untapped resource.

The themes that arose from the focus groups with service users and pharmacists were incorporated into the development of the MM and CM interventions, as discussed in subsequent sections of this chapter.

## Patient and public involvement

Following the focus groups with service users, we met with the King's College London Addiction Department Service User Research Group (SURG) to discuss the MM and CM interventions in more detail. We presented the group with examples of three different CM schedules to initiate discussions of the monetary value and type of schedule (fixed vs. escalating schedule). The group expressed the importance of the simplicity of the CM schedule, finding CM schedules that used an escalating reset design too complex and difficult to follow. However, the group did see the value in receiving an increasing amount of incentive for completion of each session, suggesting it would enhance motivation through feeling more valued. The idea of including a bonus for completion of a set number of calls was discussed, with the group believing it would also help with motivation. The group expressed concern with including a reset of the monetary value for missed calls. They believed that it may be detrimental for those who are already vulnerable, with them feeling they were being punished, which could lead to treatment dropout or relapse. The type of incentive was discussed and the group stressed the importance of the incentive being of value to the individual. The group suggested the incentive could be something personal to the individual and that this could be identified at the start of treatment as a goal to work towards. The term 'Contingency Management' was not favoured by service users who participated in the focus groups. This term was discussed with the SURG and the idea of calling it a 'Personal Achievement Award' was raised. The idea of text messages to reinforce the CM value obtained and as a practical reminder of future MM sessions was discussed. The frequency and length of the MM calls were discussed. The group were happy with the number of calls and agreed with the more intensive support at the start when a person may need it most. There was a preference for continuity in the pharmacists delivering the intervention to allow rapport and trust to be built.

## Developing the interventions

### Medication Management

The focus groups with service users and pharmacists highlighted the importance of clear guidance but with room for the conversation to be led by the needs of the service user. The importance of excellent communication skills and knowledge of alcohol dependence was also noted. This was incorporated into the guidance documents produced and the pharmacist training (see Project Webpage Document). Treatment goals were identified during the welcome call to help tailor the intervention to the participants' needs. A printed summary letter was sent to participants that they were encouraged to edit and goals were revised during the subsequent calls. We developed a partnership with Celesio/Lloyds Pharmacies who provided essential input into how the MM calls were delivered. They suggested using a call centre with a small pool of specially trained pharmacists to deliver the intervention. This allowed continuity of the pharmacist delivering the intervention for participants, which had been highlighted as important during both the focus groups and meeting with SURG for building rapport. Text message reminders were also incorporated as suggested by SURG. The length and number of MM sessions were guided by the original<sup>48,93</sup> MM manual as well as conversations with SURG and Celesio/Lloyds pharmacies, with a longer initial 'welcome call' (~30 minutes) followed by shorter (10–15 minutes) follow-up calls weekly for 6 weeks, fortnightly for 6 weeks and monthly for 3 months (12 calls in total). More frequent calls were completed at the start of treatment when the greatest support may be required with calls becoming less frequent over the 6-month period.

### Contingency Management

To maximise the effectiveness of CM, three key principles have been identified in the research literature: clear and objective verification of the treatment goal, immediacy of the reinforcement and significant

magnitude of the reinforcement.<sup>102,103</sup> These principles were taken into consideration in conjunction with the results of the focus group and patient and public involvement work when developing the CM schedule (see [Chapter 3](#), [Table 3](#)).

### Clear and objective verification of the treatment goal

For the current study, the treatment goal to be incentivised using CM was completing the MM telephone calls. A standard text message was developed that was sent on completion of each of the MM calls to all participants in the MM or the MM + CM group. The text message sent to those in the MM + CM group included information on the amount of incentive awarded for completion of that particular call and the total amount of CM achieved to date. Through speaking with the SURG group, it was clear that in order to maintain motivation of participants avoiding penalising participants was key. For example, there was concern that if calls were missed due to reasons out of participants' control, they would be unfairly penalised. To help mitigate this, a clear missed call decision tree was developed that allowed some flexibility in completion of the calls while maintaining the core components of the CM (see Project Webpage Document for the missed call decision tree). This procedure was made clear to participants in the initial welcome call and text messages were used to alert participants when calls were missed and when the next call attempt would be made.

### Immediacy of the reinforcement

During the focus groups, service users expressed mixed opinions on when the incentive should be given, after each call, periodically throughout the study or all at the end. Due to the discussions with service users attending the focus groups and the SURG about working towards a goal, and for practical reasons, it was decided that the full voucher incentive would be given to participants following the final MM call. However, participants were given the option to receive the CM incentive that they had achieved earlier if preferred. To reinforce achievement of the CM incentive, participants were informed by the intervention pharmacists of the CM incentive achieved for completing that particular call and the total incentive achieved, and they additionally received a text message as described above.

### Significant magnitude of the reinforcement

Through the focus groups and our discussions with the SURG the importance of the personal value, as opposed to financial value, of the CM incentive was highlighted. Due to practicalities, we could not tailor the CM incentive to each participant. *Love to Shop* vouchers were chosen as the incentive as they have a wide choice of shops as well as family days out. In the initial welcome call discussion, the intervention pharmacists encouraged participants to set personal goals for the CM incentive, identifying what they may wish to purchase with the voucher. This was also reinforced by the use of the term 'Personal Achievement Award' that was used in all communication with participants in line with the suggestions made in the focus groups and SURG group meeting. The monetary value of completing each MM call was based on the discussions had with the SURG and included an escalating bonus (see [Chapter 3](#), [Table 3](#)).

## Developing pharmacist training

Detailed training manuals were developed for the MM and CM interventions, including welcome call and the weekly/fortnightly/monthly calls (see Project Webpage Document). An initial two-day face-to-face training was completed with the intervention pharmacists. The training consisted of a general overview of the ADAM trial, Good Clinical Practice, discussion of the pharmacist's experience of supporting those with an alcohol problem and a demonstration of how to administer the MM calls (with feedback and questions). The intervention pharmacists were then given the opportunity to practice delivering the MM calls, which were audio-recorded to allow peer and research team assessment and feedback. At the end

of the two-day training, the intervention pharmacists completed an assessment where they role-played completion of an MM and an MM + CM call. The scenarios were identical for each pharmacist and were assessed by members of the ADAM study team using an assessment tool developed by the ADAM study team (see Project Webpage Document). This was a summative assessment, with feedback and guidance given to the intervention pharmacists. Two further refresher training sessions were completed with the intervention pharmacists during the trial, and additional training sessions with a clinical psychologist specialising in addictions were completed. These were informal sessions that were led by the needs of the intervention pharmacists. In addition, each month 10% of the completed MM calls were assessed by trained members of the research team for fidelity to the intervention. Verbal and written feedback was given to the intervention pharmacists to support intervention fidelity.

## Chapter 3 Trial methods

Material throughout the chapter has been adapted from the trial protocol.<sup>1</sup>

### Design and theoretical/conceptual framework

The study was a three-arm, parallel-group pragmatic, randomised controlled trial. The trial began with an internal pilot phase to demonstrate that recruitment, randomisation and the interventions were implemented as planned. The methodology of the pilot phase and the full trial were identical allowing for data collected during the pilot trial to be included in the statistical analyses of the primary and secondary outcomes on completion of the full trial.

Participants were prescribed acamprosate by participating in local specialist alcohol treatment services as soon as possible after alcohol abstinence was achieved. Follow-up contacts with the research team took place 6 (+60 days follow-up window) and 12 months (+60 days follow-up window) post randomisation. Participants collected their medication monthly from the community pharmacy, dispensed from designated pharmacies in bottles fitted with MEMS Caps. Eligible and consenting participants were randomised to receive either SS or SS plus MM (SS + MM) or SS plus MM and CM (SS + MM + CM). Allocation was conducted in the ratio of 2 : 1 : 1, SS : SS + MM : SS + MM + CM, respectively.

#### *Treatment arm 1: Standard Support*

All participants in the trial were prescribed acamprosate (two 333mg tablets morning, afternoon and evening if the service user's body weight was 60kg or above, or two 333mg tablets in the morning and one 333mg tablet in the afternoon and evening if the service users body weight was below 60kg, according to the manufacturer's Summary of Product Characteristics) as soon as possible following alcohol abstinence in addition to the psychosocial care normally provided. The decision to initiate acamprosate was determined by the treating clinician in the specialist alcohol service in conjunction with the service user.

Based on the current service provision of the five study centres, SS comprised monthly dispensing of prescribed acamprosate from the Lloyds community pharmacy, monthly monitoring of the service user for 3 months by the specialist alcohol service, and then returned to the care of their GP for monthly monitoring in accordance with the NICE guidelines<sup>104,105</sup> and current NHS clinical practice.

#### *Treatment arm 2: Standard Support plus Medication Management (SS + MM)*

Participants followed the same care pathway as those in the SS arm of the trial with the addition of MM, which was delivered by a central telephone support service by trained pharmacists. The MM intervention was adapted from the Medical Management intervention developed by Pettinati *et al.*,<sup>106</sup> for the Testing Combined Pharmacotherapies and Behavioral Interventions in Alcohol Dependence study, a randomised controlled clinical trial of naltrexone and acamprosate for alcohol dependence. A freely available comprehensive manual was published by the Testing Combined Pharmacotherapies and Behavioral Interventions in Alcohol Dependence research group. This was used as a basis for the MM intervention for the proposed research. Adaptation was 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 service, delivered by trained pharmacists (see [Chapter 2](#)).

MM was delivered once a week for the first 6 weeks, reducing to once a fortnight for the following 6 weeks, and then monthly for 3 months, following the same schedule as the Testing Combined Pharmacotherapies and Behavioral Interventions in Alcohol Dependence study. MM was delivered by telephone by a trained pharmacist based in a central telephone support service in the UK provided by Celesio/Lloyds Pharmacy. The initial MM session lasted approximately 30–45 minutes and acted

as a foundation for the subsequent sessions, which lasted approximately 10–15 minutes each. Each participant was assigned a specific pharmacist based in the central telephone support service to deliver each of the MM sessions for that participant where possible. The pharmacist sent a text message reminder the day before the appointment and called the participant to deliver the MM session at an agreed time.

MM provided 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 were identified to tailor the intervention to the participant and an individual plan for maintaining adherence was developed with the participant in the initial session to guide the successive MM sessions. Over the 6-month period, the pharmacist sent four summary letters to the participant highlighting the participant's individual aims, goals and key information regarding their MM plan.

### ***Treatment arm 3: Standard Support plus Medication Management with Contingency Management (SS + MM + CM)***

Evidence shows that there can be barriers to participation in MM sessions.<sup>107</sup> To optimise attendance, participants in this arm followed 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 *Love to Shop* vouchers (not redeemable for alcohol) were provided to reinforce attendance at MM sessions by telephone with the pharmacist. The CM procedure and value of the incentives have been informed by the available literature on CM in substance use disorder<sup>80</sup> and alcohol dependence<sup>104</sup> and focus groups with service users with experience with treatment services for alcohol dependence (see [Chapter 2](#)).

Participants received £5 in the form of a voucher for each MM session completed. In addition, they received a £10 bonus voucher for completing four calls in succession, a £20 bonus for completing eight calls and a £30 bonus for completing all 12 calls, with a total value of up to £120 for completing all support sessions (see [Table 3](#)). After each MM session, a SMS text message was sent to the participant to inform them that they had been awarded a voucher, the magnitude of the voucher and the total voucher value received to date. Vouchers were given on completion of the 6-month follow-up visit by the research team unless the participant withdrew from the trial or requested part payment earlier.

**TABLE 3** Contingency Management incentive schedule

Sessions completed	Incentive	Bonus	Running total
1	£5		£5
2	£5		£10
3	£5		£15
4	£5	£10	£30
5	£5		£35
6	£5		£40
7	£5		£45
8	£5	£20	£70
9	£5		£75
10	£5		£80
11	£5		£85
12	£5	£30	£120
<b>Total</b>	<b>£60</b>	<b>£60</b>	<b>£120</b>

## Study setting/context

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

## Target population

Abstinent alcohol-dependent adults within the first month of prescription of acamprosate and who were both willing and able to provide informed consent to take part in the research.

## Inclusion/exclusion criteria

Inclusion and exclusion criteria were selected to recruit a sample that is broadly representative of target population as a whole. The decision to prescribe acamprosate was made by the service users treating clinician in conjunction with the service user; the research team was not part of this decision.

### Inclusion criteria

- Adult, aged 18 years or older.
- An *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision, diagnosis of alcohol dependence.
- Abstinent from alcohol at baseline assessment.
- In receipt of a prescription for acamprosate.
- Willing and able to provide informed consent.

### Exclusion criteria

- Diagnosis of a severe physical/mental illness likely to preclude active participation in treatment or follow-up.
- Unable to understand verbal English at a level necessary to engage in the intervention and follow-up assessments.
- Concurrent dependence on an illicit substance (other than cannabis).

## Study entry and baseline assessment

Potential participants were initially contacted by a member of their specialist alcohol service, who sought permission for a member of the research team to contact the patient. The research team member subsequently contacted the patient to provide details of the nature and purpose of the research and an information sheet. Informed consent and inclusion/exclusion criteria were reviewed by a trained researcher at an initial assessment appointment that took place at least 24 hours after the study information sheet was given, to allow time to consider the information and ask any questions. Participants were then randomised by an independent party using a secure randomisation system, following consent and baseline assessment.

## Withdrawal of participants

It was made clear to participants that the SS that they receive would not be affected by their decision whether or not to take part in the research and they were free to withdraw at any time for any reason. Data collected up to the time of withdrawal would be used as appropriate unless the participant

specifically requested that the data already collected was destroyed. Withdrawn subjects were replaced as far as possible within the constraints of the duration of recruitment. If the decision not to continue prescribing/taking acamprosate was made at any stage of the trial, participants were withdrawn from the treatment and scheduled outcomes collected.

## Alcohol abstinence

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

## Randomisation

Randomisation was in the order of 2 : 1 : 1 to maximise the utility of resources with twice as many being allocated to the SS group than the two intervention groups. Randomisation was carried out after consent had been gained and the initial baseline assessment had been conducted. A remote randomisation procedure was used through an online system developed and maintained by the company Codeface Ltd to generate the treatment allocation, which was initiated by a trained researcher. Allocation employed a stratified random permuted block method with stratification by severity of alcohol dependence [Severity of Alcohol Dependence Questionnaire (SADQ) score of  $\leq 30$  or  $> 30$ ], research site and the prescription of other relapse prevention medication. These variables are known to be related to clinical outcomes and were collected at the baseline assessment. Due to the nature of the trial, participants and research staff were not blind to treatment allocation. The trial statistician was blind to treatment allocation.

## Data collection and management

[Table 2](#) outlines the study outcome measures and timing of their administration during the study. Research and personal data were collected using electronic data capture, specifically designed for this research study, using a laptop computer. Laptop computers were password protected. Data were entered and saved on a secure server with a 256-bit encryption (SSL/https) connection; no data were saved directly onto the laptop computer. Research data were anonymised by assigning each participant a unique ID number, with personal data stored separately from the research data to maintain participant anonymity. The Chief Investigator, Trial Manager and Trial Statistician have access to the final full data set.

## Outcome measures

The primary outcome measure was the self-reported percentage of medication taken as prescribed during the 6-month target phase of prescribing, post randomisation.

### Secondary outcome measures

Secondary, process and economic outcome measures are detailed in [Table 4](#). At baseline assessment, participant demographics were 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)<sup>104</sup> was administered to obtain a history of any substance use.

Severity of dependence was measured at the baseline assessment and at 6- and 12-month follow-ups using the SADQ.<sup>108</sup> The SADQ is a 20-item self-complete questionnaire containing items representing five domains of the alcohol dependence syndrome: (1) physical withdrawal signs, (2) psychological withdrawal signs, (3) withdrawal relief drinking, (4) tolerance and (5) reinstatement following a period of abstinence.

**TABLE 4** Trial outcome measures, timing of administration and duration of participant completed questionnaires

	Baseline	Months 2 and 4	Month 6	Month 12
Clinical outcomes				
MEMSCap		✓	✓	✓
Pharmacist pill count		✓	✓	
Past 28 days adherence self-report		✓	✓	✓
MMAS-8		✓	✓	✓
SADQ	✓		✓	✓
AUQ	✓		✓	✓
TLFB 28 days	✓		✓	✓
Economic outcomes				
Health-related quality of life (EQ-5D-5L)	✓		✓	✓
AD-SUS	✓		✓	✓
Prognostic outcomes				
Demographics	✓			
BMQ	✓		✓	✓
APQ	✓			
STAR			✓	

AD-SUS, Adult Service Use Schedule; APQ, Alcohol Problems Questionnaire; AUQ, Alcohol Urge Questionnaire; BMQ, Beliefs about Medications Questionnaire; EQ-5D-5L, EuroQol-5 Dimensions, five-level version; MMAS-8, Morisky Medication Adherence Scale; STAR, Scale to Assess Therapeutic Relationship; TLFB, Time-Line Follow-Back.

Alcohol consumption was measured using the TLFB Form 90,<sup>109</sup> administered at initial baseline assessment and at 6- and 12-month follow-ups after initiation of acamprosate. Percentage days abstinent, units of alcohol per drinking day (1 UK unit = 8 g alcohol), relapse to any drinking and relapse to heavy drinking (8+/6+ units for males/females on a single occasion) were derived.

Participants' beliefs about medications were assessed using the BMQ.<sup>110</sup> 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 was administered at baseline assessment and at 6-month follow-up. The measure was also used to evaluate the impact of MM on beliefs and concerns about medication and the association with adherence to acamprosate. The MMAS-8 assesses non-adherence and was administered at months 2, 4, 6 and 12.<sup>111–113</sup>

Participants in the SS + MM and SS + MM + CM groups were asked to rate their therapeutic relationship with the telephone pharmacist at 6 months using the STAR rating scale.<sup>114</sup> Therapeutic relationship (or alliance) has been found to predict clinical outcome across a range of mental disorders<sup>115</sup> including alcohol dependence.<sup>116</sup> This was used as an additional process measure to explore the impact of therapeutic relationship on medication adherence and clinical outcome.

Alcohol-related problems were assessed at baseline assessment using the APQ.<sup>8</sup> 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 AUQ<sup>117</sup> assesses current urge for alcohol using eight items which cover three factors: desire for a drink (four items); expectation of positive effect from drinking (two items) and inability to avoid drinking if alcohol was available (two items). This questionnaire was administered at baseline assessment and at 6- and 12-month follow-ups.

Measures for the economic evaluation, collected at baseline, 6- and 12-month follow-ups, included the EQ-5D-5L measure of health-related quality of life<sup>118</sup> suitable for the calculation of QALYs and the AD-SUS, based on a version designed for use in alcohol and drug populations<sup>119</sup> and adapted for the purpose of the ADAM trial. These measures are described in more detail in [Chapter 5](#).

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

## Fidelity of intervention delivery

The fidelity of delivery of MM and CM and its impact on acamprosate adherence and clinical outcomes was assessed. All MM sessions were audio-recorded. A random sample, stratified by pharmacists delivering the intervention, of 10% of all audio recordings of each of the MM and MM + CM interventions were rated by at least two trained raters who were members of the research team, using a checklist of required elements. The raters were supervised by the postdoctoral research pharmacist and the trial manager through regular meetings. The postdoctoral research pharmacist and trial manager checked 10% of the fidelity ratings completed. The information gained from checking the fidelity ratings was fed back to the raters during the regular supervision meetings to ensure as much accuracy as possible of the fidelity assessments. The information from the fidelity assessments was fed back to the pharmacists delivering the MM and CM to improve intervention fidelity.

## Sample size

A clinically important difference in adherence to medication was estimated as an effect size of the order of 0.3, equivalent to a 12% difference in medication adherence between the groups and a number needed to treat of 8 for drinking outcomes, in that if any intervention strategy is found to be superior eight participants would need to be treated to create an additional participant who is abstinent. A meta-analysis<sup>120</sup> 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. As with all pragmatic studies final interpretation was based on actual effects observed and the integration of economic outcomes, but an effect size of < 0.3 is unlikely to be clinically important.

To estimate this difference using power of 80%, alpha 0.05 with a two-sided tested and differential allocation of 2 : 1 : 1 required 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, required a total sample size at allocation of 748; 374 allocated to SS, 187 to SS + MM and 187 to SS + MM + CM. In addition to addressing the primary outcome, the sample size was sufficient to identify a clinically important difference effect size of 0.3 in alcohol consumption measures at 6 months post randomisation.

## Statistical analysis

The primary analysis is based on the analysis by treatment allocated (ATA) where participants are analysed as members of their allocated group irrespective of the treatment they receive; this provides a conservative estimate of effect. Secondary analyses examined treatment effects under different scenarios for compliance with allocation/treatment: complier average causal effects (CACE). Two scenarios of compliance were defined in this trial. In the first compliance, those in the SS + MM and SS + MM + CM group was defined as adhering to at least 50% of the MM calls. In the second, the threshold was increased to 100%. Both scenarios are modelled in the analysis.

The different scenarios of compliance with allocation for this trial are shown in [Table 5](#). There are two scenarios according to the number of calls received. Under the first scenario those receiving 6 or more

**TABLE 5** Compliance according to group allocation vs. treatment received

Allocated	Received	
	SS + MM/SS + MM + CM	Control
SS + MM	A. <i>Treatment complier</i>	B. <i>Treatment non-complier</i>
SS + MM + CM	Scenario 1: Received 6 or more calls Scenario 2: Received 12 or more calls	Received < 6 calls Received < 12 calls
Control	C. <i>Control non-complier</i> N/A	D. <i>Control complier</i> Control group participant

calls are considered 'compliers' in the active treatment groups and those receiving fewer than 6 calls are considered non compliers. Under scenario 2, those in the active treatment groups receiving 12 or more calls are considered compliers and those who receive fewer than 12 calls are considered non-compliers. (2) As all participants in the active treatment groups also received the control treatment, all non-compliers in the treatment group are regarded as being 'contaminated'. For the control group, there is no option for control participants to access the intervention, so there cannot be non-compliance, cell C.

### Analysis by treatment allocated

Analyses all available data for participants who were randomised, regardless of whether they complied with allocation. This data set includes participants who were withdrawn from the trial post randomisation. These analyses are a lower bound estimate of treatment effects as they represent the effect of offering an intervention, rather than the effect of receiving that intervention.

### Complier average causal effects

We assessed treatment effects in the presence of non-compliance, with compliance measured at the individual level and including all those allocated as part of the trial. Our approach for assessing treatment effects under non-compliance was via the instrumental variables (IV) framework.<sup>121</sup> The benefit of using an IV approach is that randomisation is maintained in the analysis, which is crucial for estimating unbiased treatment effects.<sup>122</sup> CACE weights the ATA treatment effect by the proportion of compliers (see [Equation 1](#)):

$$\text{CACE} = \frac{\text{ATA}}{\text{proportion compliant}} \quad (1)$$

If the proportion compliant is 1.0 (i.e. perfect compliance), then the CACE estimate is the same as the ATA estimate, but otherwise the impact of this approach is to increase the magnitude of the treatment effect.

Complier average causal effects use a two-stage least squares (2SLS). The first stage model uses treatment received (T) as the outcome, with random allocation (Z) as the independent variable (see [Equation 2](#)):

$$T = \alpha + Z \quad (2)$$

Based on the stage 1 model, we then calculate predicted values of treatment received ( $\hat{T}$ ) for use in stage 2. The second stage model predicts the substantive outcome (Y, e.g. days abstinent) using the predicted values of treatment received ( $\hat{T}$ ) based on the stage 1 model (see [Equation 3](#)):

$$Y = \alpha + \hat{T} + \varepsilon \quad (3)$$

The CACE analysis was conducted using 2SLS estimation with the ivregress command in Stata® (StataCorp LP, College Station, TX, USA). A linear regression approach was used to assess per cent adherence with medication and per cent days abstinent from alcohol at 6 months post randomisation.

### Missing data

The proportion of missing data and patterns of missingness were examined for the primary outcome, per cent adherence to medication at month 6. Levels of missing data are reported along with any systematic occurrences of missing data observed in the data sets. Where outcomes are derived scores, individual item scores were checked for systematic missingness by comparing the proportion of missing values by SADQ category ( $\leq 30$  and  $> 30$ ), current prescription of relapse prevention medication, community alcohol treatment service and allocated group.

To avoid loss of efficiency, we imputed missing primary outcome values using multiple imputation using the MI commands of Stata; we employed 50 iterations of a multiple imputation model and combined these using MIcombine. We then tested the extent to which the imputed model deviates from the model generated using the observed data. This approach makes an underlying assumption that the missing data are missing at random (MAR). To test a potential assumption that data were not missing at random (MNAR), we conducted a sensitivity analysis using a pattern mixture approach and multiple imputation to explore the sensitivity of the primary outcome results to departures from the MAR assumption, and this was implemented using the rctmiss command in Stata.<sup>123,124</sup>

### Statistical analysis methods

Analysis of the study is presented in accordance with CONSORT guidelines.<sup>125</sup> The primary analysis is an ATA and is based on all available data for participants who were randomised, irrespective of whether they complied with their allocation or not.

Diagnostic tests and plots were conducted to assess the assumptions of normality for per cent adherence to acamprosate at month 6. There were significant departures from normality (Project Webpage Document) and the distribution overall and by group was a bimodal distribution with a zero-inflation. As the primary outcome is a percentage, it can be recalculated as a proportion between 0 and 1 by dividing the per cent adherence by 100. The fractional nature of the outcome allows for a fractional logistic model<sup>126</sup> to be fitted, assuming the variance in response is proportional to a binomial distribution, and employing a logit link function to maintain bounds between 0 and 1. Fixed effects were included for allocation (SS/SS + MM/SS + MM + CM) and stratification covariates (SADQ;  $\leq 30$  or  $> 30$ , other relapse prevention medication; yes or no, site). Results are initially presented as odds ratios, but marginal effects can be derived to present the mean difference in per cent adherence between the groups and the associated 95% CI. Secondary analysis of the primary outcome encompasses multiple imputation to assess missing data as MAR, sensitivity analysis to assess missing data being MNAR and inclusion of data on adherence to allocated intervention using two pre-specified scenarios incorporated into a CACE analysis. Analysis was undertaken to explore differences between SS + MM + CM versus SS and then to explore differences between SS + MM versus MM. As significant effects were observed on the primary outcome measure, an analysis exploring SS + MM + CM versus SS + MM was then undertaken.

Secondary outcomes are analysed in a similar manner by assessing distributional assumptions and conducting an appropriate regression with the inclusion of the same covariates as the primary analysis. Where baseline values for the secondary outcome are available, these are also included as covariates.

Stepwise regression was conducted to model the between pre-randomisation factors and per cent adherence to Acamprosate and per cent days abstinent at month 6. Interaction terms with treatment allocation were included in the model and a significance level of 0.1 was used as a threshold to determine which variables were maintained in the final model reported. Baseline variables included initially in the model include age, gender, marital status, ethnicity, employment status, number of children, age of first drink, weekly and daily drinking, frequency and quantity of alcohol consumption, severity of alcohol dependence, alcohol urges and alcohol-related problems. This analysis was augmented with an additional analysis for the SS + MM and SS + MM + CM groups where the same dependent variable was assessed with the same independent variables with the addition of therapeutic alliance.

## Economic analysis

Please see [Chapter 5](#) for full details of the health economic evaluation.

## Safety reporting

A serious adverse event (SAE) is defined as an untoward occurrence that:

1. results in death
2. is life-threatening
3. requires hospitalisation or prolongation of an existing hospital stay
4. results in persistent or significant disability or incapacity
5. consists of a congenital anomaly or birth defect, or
6. is otherwise considered medically significant by the investigator.

The Chief Investigator reported any SAE to the Research Ethics Committee (REC) who provided ethical opinion within 15 days of becoming aware of the event if the event was related (i.e. resulted from administration of any of the research procedures), and unexpected (i.e. the type of event is not listed in the protocol as an expected occurrence). The Chief Investigator reported on the safety of participants in the annual progress report to the REC.

## Ethics and dissemination

The trial was 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). At each research appointment (baseline assessment, 6- and 12-month follow-ups), all participants were given £10 cash to compensate them for their time, plus travel expenses.

Participants' anonymity was preserved throughout using code numbers for all data collection. Data were anonymised and stored by secure means (password-protected computers/laptops, locked filing cabinets in lockable offices in buildings with swipe access and security presence).

Ethical approval has been granted by the East of England – Cambridge South Research Ethics Committee (Ref: 15/EE/0308). All participants gave written informed consent to take part in the research.

## Monitoring

An independent Steering Committee was set up and approved by the National Institute for Health Research. An independent Data Monitoring Committee was set up and included an independent statistician who is not otherwise involved in the project. A trial management group met regularly to monitor the progress of the trial. This group included the Chief Investigator, the Principal Co-Investigators, the researchers, clinicians and service user representative.

## Amendments

During the trial, six substantial amendments were made to the trial protocol, [Table 6](#) details these amendments and the rationale for each. No amendments affected participant safety.

**TABLE 6** Trial protocol amendment history

Version	Date	Amendment	Rationale for amendment
1.0	21 July 2015	N/A	N/A
2.0	18 November 2015	Inclusion of a summary letter to participants receiving MM	The summary letter provided a visual reminder of the aims, goals and key information of the participant's MM plan
3.0	05 September 2016	Additional acamprosate supply reporting questions	To capture instances when participants receive additional emergency supplies of acamprosate – e.g. when admitted to hospital or an emergency supply from a pharmacy
4.0	02 May 2017	Extension of data collection window to 60 days at 6- and 12-month follow-up	To maximise data collection by extending the time frame for follow-up
5.0	20 June 2017	Removal of current dependence on cannabis use as an exclusion criterion	To maximise participant recruitment. Following advice from the Trial Management Group, it was felt that cannabis use would not hinder the efficacy of the trial interventions but was negatively impacting on recruitment
6.0	13 May 2019	Removal of the 12-month follow-up assessment	To maximise participant recruitment. The 12-month follow-up assessment was removed to extend the recruitment period without extending the trial end-date
7.0	21 July 2020	Clarification of the 12-month data analysis	Removal of the 12-month follow-up period was not intended to alter the data analysis plans. Clarification to the working of protocol V6 to reflect this was therefore made

### *Deviations from the statistical analysis plan*

The APQ was not collected at 6 and 12 months, which is a deviation from the trial protocol. In addition, two key changes were implemented that deviated from the statistical analysis plan. These changes were agreed with the trial steering committee.

#### *1. Measuring the primary outcome*

Our primary outcome was per cent adherence to acamprosate at month 6. At the design stage, we explored the current literature on measuring adherence and settled on a hierarchy of measure. Our first measure was to be the MEMS, where medication is placed in a pill bottle and a cap measures every time the cap was opened. As acamprosate is taken in three daily doses (666 mg three times per day or 666 mg once followed by 333 mg twice a day), we planned to calculate the denominator as the number of days in the period between baseline and month 6 multiplied by three and the numerator the number of MEMS registered openings; this would allow an objective measure of adherence. At month 6, MEMS data were available for 514 participants, 70%, yet only one participant was 100% adherent and the majority, 383 (75%) had zero adherence with a mean adherence of 23% (95% CI 21% to 26%). Exploration of qualitative notes taken at the time of follow-up suggested large numbers of participants complied with their medication but found the MEMS device inconvenient and cumbersome, rather than taking medication out of the device many either stopped using it at all or took their daily medication out on a weekly basis. An alternative objective measure was pill counts conducted by the pharmacist when participants came to collect their prescribed medication, but it was clear early in the trial that this method was fraught with complications. Many participants did not actually attend the pharmacy to collect medications, those that did often did not bring their remaining pills for counting and when pill counts were conducted, they often failed to include details of what medication had been previously dispensed. Pharmacy pill counts were not considered a reliable source of adherence

data. Our third source of adherence data was self-report, where we asked participants at month 6 to estimate the per cent of days they had been adherent to medication in the past 28 days. At month 6, self-report data were available for 514 participants, 70%, of whom 257 (50%) stated they had been completely non-adherent, 70 (15%) had been 100% adherent and the mean adherence was 42% (95% CI 38% to 46%). There was a mean difference between self-report and MEMS of 12.3% (95% CI 8.7% to 15.9%). Considering the known issues with the MEMS data, we decided to use the self-report adherence as the primary outcome. Our reasoning was based on evidence that in the trial, the MEMS device underestimated adherence, evidence that self-report is a valid and reliable method for estimating adherence<sup>127</sup> and that self-report estimates over shorter period are reliable proxies for adherence over longer periods for those with chronic conditions.<sup>128</sup>

## 2. *Exploring the impact of participants being followed up late at the month 6 primary end point*

In our trial protocol, we stated that the primary end point would be 6 months after randomisation. As we are dealing with a relatively hard-to-reach group, we allowed a window of + 60 days around the 6-month follow-up point. It became apparent prior to analysis that some participants had 6-month follow-up assessments conducted later than 6 months plus 60 days. We identified 45 participants that fell into this group, 9% of those followed up at month 6. Exploring baseline variables for those followed up late versus those not, identified no differences in terms of demographics, allocation, or outcomes (Project Webpage Document). We did note that the majority of those followed up late indicated zero adherence to acamprosate at month 6, 34 out of 45 (76%). To place maximum confidence on our findings, we proposed to include an additional sensitivity analysis of the primary outcome where we include and exclude these participants to explore any impact of late follow-up on the outcomes observed.



## Chapter 4 Trial statistical analysis

A full CONSORT diagram is presented in [Figure 1](#). Participant recruitment took place between July 2016 and December 2019, and participant follow-ups were completed in July 2020. A total of 1459 potential participants were approached of whom 1019 (70%) were assessed. Of these, 739 (73%) were eligible and consented to participate in the study. Allocation was in the ratio of 2 : 1 : 1, 372 (50%) were allocated to SS, 182 (25%) to SS + MM and 185 (25%) to SS + MM + CM. At the primary end point, 6 months post randomisation, 518 (70%) were successfully followed up. Seventy-five serious adverse events were reported during the trial (including 16 deaths), none of which were considered to be related to the trial interventions.

Of those allocated to one of the intervention groups, 105 (58%) adhered to 50% of the MM calls in the SS + MM group and 128 (69%) in the SS + MM + CM group. Compliance with 100% of MM calls also differed by allocated group with 20 (11%) complying in the SS + MM group and 73 (39%) complying in the SS + MM + CM group. The allocation method appears to have worked with no observed differences in demographics (see [Table 7](#)) or baseline outcomes (see [Table 8](#)) between the groups at baseline.

Approached 1459			Not assessed 440	
			Not contactable 167	
			Declined participation 273	
Assessed 1019			Excluded 279	
			Not meeting criteria 209	
			Declined 59	
			Other 12	
Consent and allocated 739				
SS 372 (50.3%)	SS+MM 182 (24.7%)	SS+MM+CM 185 (25.0%)		
Month 2 230 (61.8%)	Month 2 108 (59.4%)	Month 2 123 (66.5%)		
Month 4 219 (58.9%)	Month 4 101 (55.5%)	Month 4 118 (63.8%)		
Month 6 255 (68.5%)	Month 6 122 (67.0%)	Month 6 141 (76.2%)	Withdrawals 37	
			SS 18	
			SS+MM 11	
			SS+MM+CM 8	
Month 12 191 (51.3%)	Month 12 95 (52.2%)	Month 12 102 (55.1%)		

**FIGURE 1** Alcohol Dependence and Adherence to Medicine trial CONSORT diagram.

**TABLE 7** Baseline demographics by allocated group

	SS + MM + CM (n = 186)	SS + MM (n = 182)	SS alone (n = 372)	Overall (n = 740)
Site, n (%)				
Birmingham	57 (30.7)	55 (30.2)	111 (29.8)	223 (30.1)
C&NW London	38 (20.4)	40 (22.0)	78 (21.0)	156 (21.1)
South East London	19 (10.2)	16 (8.8)	38 (10.2)	73 (9.9)
Southampton	22 (11.8)	24 (13.2)	48 (12.9)	94 (12.7)
Yorks & Humber	50 (26.9)	47 (25.8)	97 (26.1)	194 (26.2)
Mean age [standard error (SE)]	45.9 (0.74)	46.7 (0.75)	46.2 (0.55)	46.2 (0.38)
Male, n (%)	114 (61.3)	109 (60.2)	226 (60.8)	449 (60.8)
Ethnicity, n (%)				
White	153 (82.3)	154 (84.6)	317 (85.2)	624 (84.3)
Black	13 (7.0)	9 (5.0)	14 (3.8)	36 (4.9)
Asian	13 (7.0)	13 (7.1)	23 (6.2)	49 (6.6)
Other	7 (3.7)	6 (3.3)	18 (4.8)	31 (4.2)
Main occupation ever, n (%)				
Professional	45 (24.9)	53 (29.4)	109 (30.6)	207 (28.9)
Skilled	57 (31.5)	53 (29.4)	107 (30.1)	217 (30.3)
Semi-skilled	32 (17.7)	37 (20.6)	64 (18.0)	133 (18.5)
Unskilled	41 (22.6)	32 (17.8)	67 (18.8)	140 (19.5)
Unemployed	2 (1.1)	4 (2.2)	3 (0.8)	9 (1.3)
Other	4 (2.2)	1 (0.6)	6 (1.7)	11 (1.5)
Current employ status, n (%)				
Full time	45 (24.3)	40 (22.0)	85 (22.8)	170 (23.0)
Part time	11 (5.9)	6 (3.3)	22 (5.9)	39 (5.3)
Unemployed/incapacity	118 (63.4)	123 (67.6)	238 (64.0)	479 (64.7)
Student	1 (0.5)	1 (0.5)	1 (0.3)	3 (0.4)
Other	11 (5.9)	12 (6.6)	26 (7.0)	49 (6.6)
Accom. status, n (%)				
Owner	63 (33.9)	44 (24.2)	104 (28.0)	211 (28.6)
Tenant	95 (51.1)	108 (59.3)	187 (50.4)	390 (52.8)
Homeless	3 (1.6)	7 (3.9)	17 (4.6)	27 (3.6)
Other	25 (13.4)	23 (12.6)	63 (17.0)	111 (15.0)
Mean number of children (SE)	1.22 (0.06)	1.21 (0.06)	1.14 (0.05)	1.18 (0.03)
Mean age first drink (SE)	14.57 (0.35)	14.41 (0.35)	14.30 (0.22)	14.4 (0.16)
Mean age week drink (SE)	20.22 (0.53)	20.24 (0.63)	20.16 (0.44)	20.19 (0.30)
Mean age daily drink (SE)	29.12 (0.83)	29.78 (0.87)	28.58 (0.61)	29.01 (0.43)
Stratification				
SADQ $\leq$ 30, n (%)	73 (39.2)	75 (41.2)	149 (40.0)	297 (40.1)
Relapse medication, n (%)	16 (8.6)	14 (7.7)	30 (8.1)	60 (8.1)

**TABLE 8** Baseline outcomes by allocated group

	SS + MM + CM (n = 186)	SS + MM (n = 182)	SS alone (n = 372)	Overall (n = 740)
ASSIST low risk, n (%)				
Tobacco	58 (31.2)	64 (35.2)	130 (35.0)	252 (34.0)
Cannabis	156 (83.9)	151 (83.0)	300 (80.9)	607 (82.1)
Stimulants	178 (95.7)	175 (96.2)	356 (95.7)	709 (95.8)
Sedatives	185 (99.5)	179 (98.4)	364 (97.8)	728 (98.4)
Opioids	181 (97.3)	179 (98.4)	370 (99.5)	730 (98.6)
Novel psychoactive	186 (100)	181 (99.4)	369 (99.2)	736 (99.5)
Mean APQ (SE)				
Friends	2.06 (0.19)	1.86 (0.27)	2.22 (0.21)	2.09 (0.13)
Finances	1.44 (0.26)	0.78 (0.26)	0.96 (0.21)	1.05 (0.14)
Police	0.31 (0.18)	0.14 (0.14)	0.33 (0.12)	0.28 (0.08)
Physical health	3.51 (0.50)	3.43 (0.49)	4.67 (0.27)	4.04 (0.24)
Affective	2.50 (0.43)	2.78 (0.32)	2.67 (0.29)	2.65 (0.20)
Common	9.84 (1.06)	9.02 (0.92)	10.85 (0.78)	10.12 (0.53)
Marital	3.69 (0.54)	3.93 (0.50)	4.18 (0.44)	3.98 (0.28)
Children	1.06 (0.32)	1.93 (0.42)	2.11 (0.31)	1.77 (0.21)
Work	3.00 (0.48)	2.14 (0.37)	2.59 (3.63)	2.60 (0.24)
Number abstinent, n (%)	2 (1.08)	0	7 (1.92)	9 (1.24)
Mean TLFB drinks (SE)	1958 (117)	1999 (195)	1831 (87)	1903 (71)
Mean PDA (SE)	33.2 (2.27)	29.9 (2.14)	32.1 (1.47)	31.8 (1.07)
Mean APD (SE)	32.8 (2.00)	31.2 (2.47)	28.8 (1.22)	30.2 (1.0)
Mean % days 6 + units (SE)	65.4 (2.31)	67.8 (2.22)	66.30 (1.52)	66.4 (1.10)
Mean % days 15 + units (SE)	60.2 (2.70)	57.6 (2.76)	57.3 (1.84)	58.1 (1.33)
Mean AUQ (SE)	1.85 (0.09)	1.84 (0.09)	1.64 (0.05)	1.74 (0.04)
Mean BMQ (SE)				
Specific	26.5 (0.41)	26.2 (0.45)	26.1 (0.29)	26.2 (0.21)
General	20.7 (0.39)	21.2 (0.38)	20.8 (0.26)	20.8 (0.19)
Mean SADQ (SE)	33.7 (0.96)	32.9 (1.02)	33.5 (0.71)	33.4 (0.50)
SADQ status, n (%)				
Mild	19 (10.2)	24 (13.2)	42 (11.3)	85 (11.5)
Moderate	54 (29.0)	51 (28.0)	107 (28.8)	212 (28.6)
Severe	113 (60.8)	107 (58.8)	223 (59.9)	443 (59.9)
Mean EQ-5D-5L utility (SE)	0.79 (0.01)	0.80 (0.01)	0.81 (0.01)	0.80 (0.01)
Mean EQ-5D-5L visual analogue scale (SE)	64.7 (1.41)	65.3 (1.39)	65.5 (1.04)	65.3 (0.72)

## Primary outcome analysis

[Table 9](#) presents the outcomes at months 6 and 12 by allocated group (see [Appendix 1, Table 23](#) for outcomes by allocated group at 2 and 4 months). To conduct a fractional regression using per cent adherence to acamprosate at month 6, a fractional outcome was generated by dividing the outcome by 100. Fractional regression, with a logit link function, was conducted using the *fracreg logit* command in Stata, allocation and stratification variables were included as fixed effect covariates, as adherence was not available at baseline, this covariate was omitted. The odds ratio and 95% CI can be difficult to interpret so these were converted to marginal effects representing mean differences in per cent adherence to acamprosate at month 6.

The distribution of the primary outcome by allocated group is presented in [Table 10](#) and the overall distribution presented in [Appendix 1, Figure 20](#). The results of the ATA are presented in [Table 11](#).

The mean difference in per cent adherence to acamprosate at month 6 between those allocated to SS and SS + MM + CM is 10.6% (95% CI 19.6% to 1.6%) lower in the SS group than the SS + MM + CM group; this difference is statistically significant. When the SS + MM group is compared to SS alone, the SS + MM group has a lower per cent days adherent than the SS group, mean difference 3.1% (95% CI 12.8% to -6.5%), but this difference is not significant. A similar non-significant finding is seen when we compared the SS + MM and SS + MM + CM groups, mean difference 7.9% (95% CI 18.7% to -2.8%).

**TABLE 9** Outcomes by allocated group at 6 and 12 months

	Month 6			Month 12		
	SS + MM + CM (n = 141)	SS + MM (n = 122)	SS alone (n = 255)	SS + MM + CM (n = 104)	SS + MM (n = 96)	SS alone (n = 193)
Prescribed acamprosate, n (%)	88 (62.4)	63 (51.64)	130 (51.0)	27 (36.0)	21 (21.9)	54 (28.0)
Mean % adherence (SE)	49.1 (3.7)	41.2 (4.1)	37.9 (2.7)	19.5 (3.7)	17.9 (3.7)	21.6 (2.7)
Mean MMAS-8 (SE)	5.5 (0.16)	5.3 (0.18)	5.0 (0.2)	5.4 (0.2)	5.6 (0.3)	5.2 (0.2)
Number abstinent, n (%)	59 (42.5)	51 (42.9)	96 (39.5)	39 (37.9)	42 (43.8)	76 (41.3)
Mean TLFB drinks (SE)	375.3 (60.0)	544.2 (84.6)	527.1 (56.2)	553.0 (106)	537.9 (97.2)	528.6 (64.7)
Mean PDA (SE)	74.1 (3.1)	72.4 (3.5)	69.6 (2.4)	73.6 (3.6)	71.0 (4.0)	68.8 (2.9)
Mean APD (SE)	8.8 (1.1)	10.5 (1.2)	10.8 (0.8)	12.7 (1.6)	9.8 (1.3)	10.4 (0.9)
Mean % days 6 + units (SE)	21.0 (3.0)	25.2 (3.4)	27.8 (2.4)	23.7 (3.5)	26.6 (3.9)	28.6 (2.8)
Mean % days 15 + units (SE)	13.3 (2.8)	19.3 (3.3)	19.2 (2.3)	17.0 (3.1)	14.9 (3.2)	16.7 (2.5)
Mean AUQ (SE)	2.0 (0.1)	2.2 (0.2)	2.1 (0.1)	2.2 (0.2)	1.9 (0.2)	1.9 (0.1)
Mean BMQ (SE)						
Specific	20.7 (0.4)	20.7 (0.5)	21.1 (0.3)	20.1 (0.6)	20.0 (0.6)	21.3 (0.4)
General	22.8 (0.5)	21.1 (0.6)	22.2 (0.4)	19.7 (0.7)	19.0 (0.6)	20.9 (0.6)
Mean SADQ (SE)	21.2 (1.8)	25.9 (2.1)	23.1 (1.3)	21.6 (2.2)	21.1 (2.3)	24.0 (1.5)
SADQ status, n (%)						
Mild	30 (21.0)	20 (16.4)	60 (23.2)	26 (23.8)	26 (25.7)	41 (21.1)
Moderate	23 (16.1)	20 (16.4)	37 (14.3)	12 (11.0)	10 (9.9)	24 (12.4)
Severe	90 (62.9)	82 (67.2)	162 (62.5)	71 (65.2)	65 (64.4)	129 (66.5)
Mean EQ-5D-5L (SE)	0.78 (0.02)	0.80 (0.02)	0.78 (0.02)	0.83 (0.02)	0.83 (0.02)	0.80 (0.02)
Mean EQ-5D-5L VAS (SE)	67.5 (1.7)	67.1 (2.4)	63.8 (1.5)	68.6 (2.2)	66.4 (2.3)	65.0 (1.8)

**TABLE 10** Mean (SD), median and distribution for per cent adherence at month 6 by allocated group

	SS + MM + CM (n = 141)	SS + MM (n = 122)	SS (n = 255)
Mean (SD)	49.1 (44.4)	41.2 (45.7)	37.9 (43.7)
Percentiles			
1%	0	0	0
5%	0	0	0
10%	0	0	0
25%	0	0	0
Median	70	0	0
75%	95	95	90
90%	100	100	100
95%	100	100	100
99%	100	100	100

**TABLE 11** Analysis by treatment allocated (ATA) analysis indicating odds ratio, marginal effects (95% CI) of % adherence at month 6 by allocated group derived from a fractional regression (results adjusted for baseline stratification variables: SADQ, Site, Other relapse prevention prescription) (n = 514)

	SS + MM + CM vs. SS	SS + MM vs. SS	SS + MM + CM vs. SS + MM
Marginal effect			
Allocated group			
SS	-0.106 (-0.196; -0.016)*	-0.031 (-0.128; 0.065)	-
MM	-	-	-0.079 (-0.187; 0.028)
Odds ratio			
Allocated group			
SS	0.642 (0.442; 0.934)*	0.874 (0.580; 1.317)	-
SS/MM	-	-	0.719 (0.459; 1.123)
SS/MM/CM	-	-	-
Site <sup>a</sup>			
Central and North West London	0.714 (0.430; 1.186)	0.625 (0.364; 1.075)	1.428 (0.764; 2.670)
South East London	0.306 (0.142; 0.662)	0.381 (0.180; 0.808)*	0.592 (0.215; 1.634)
Southampton	0.897 (0.502; 1.602)	0.978 (0.538; 1.778)	1.406 (0.679; 2.913)
Yorks & Humber	0.912 (0.552; 1.508)	0.815 (0.482; 1.378)	1.349 (0.740; 2.457)
SADQ <sup>b</sup>	1.088 (0.745; 1.589)	1.090 (0.735; 1.616)	1.589 (1.000; 2.525)*
Current prescription <sup>c</sup>	0.815 (0.373; 1.780)	0.857 (0.382; 1.921)	0.816 (0.335; 1.984)

\*  $p \leq 0.05$ .<sup>a</sup> Reference vs. Birmingham.<sup>b</sup> Reference vs. SADQ  $\leq 30$ .<sup>c</sup> Reference vs. no baseline prescription.

### Late follow-up sensitivity analysis

Our first sensitivity analysis incorporates those who followed up on time and those who followed up late at month 6 (please see [Appendix 1, Table 24](#)). [Table 12](#) presents the results of this sensitivity analysis. There are no significant deviations from the primary analysis conducted so all participants are included in the analysis.

### Missing primary outcome data

To explore whether missing primary outcome data are MAR we conducted a logistic regression analysis to explore what variables might predict missing outcome data. Variable selection was undertaken by exploring associations at the 0.10 *p*-level. The analysis identified age, site, gender and per cent days abstinent at baseline as being predictive of missing primary outcome data. Using these predictive variables, we imputed 50 iterations of a multiple imputation model and pooled these using the *micombine* command in Stata.

We used a similar fractional regression approach as the primary analysis to generate odds ratios comparing SS + M + CM versus SS, SS + MM + versus SS and SS + MM + CM versus SS + MM. As the *mi* command set does not allow for the generation of marginal effect, we plotted odds ratios and 95% CIs for each of the comparisons in order to visually explore whether there are significant deviations between the observed and imputed values of the primary outcome. [Appendix 1, Figures 21–23](#) presents the plots and it is confirmed that the influence of missing data, based on a MAR assumption, does not influence our interpretation of the results.

To explore the influence of missing data being MNAR, we employed a sensitivity analysis to explore departures from the MAR assumption. Varying deltas of 0.1 ranging from –0.5 to 0 were employed in intervention group alone, control group alone and both intervention and control group. Analysis was undertaken using the *rctmiss* command in Stata. Visual inspection of the data indicates even at large departures from the MAR assumption the impact on the treatment effect is small; these are presented in [Appendix 1, Figures 24–26](#).

We can be confident that the treatment effects are robust under different interpretations of the nature of missing data.

### Complier average causal effects analysis

We defined our compliance criteria as two separate scenarios: scenario 1 where participants in the intervention groups adhered to at least 6 (50%) MM calls and scenario 2 where they adhered to 12 (100%). Of those allocated to one of the intervention groups, 105 (58%) adhered to 50% of the MM calls in the SS + MM group and 128 (69%) in the SS + MM + CM group. Compliance with 100% of MM calls also differed by allocated group with 20 (11%) complying in the SS + MM group and 73 (39%) complying in the SS + MM + CM group.

We conducted a CACE analysis using the *ivregress 2sls* command in Stata. The dependent variable was per cent adherence to acamprosate at month 6 adjusted for stratification covariates. [Table 13](#) presents a comparison of ATA effects and CACE effects for each of our scenarios.

**TABLE 12** Sensitivity analysis of differences in marginal means of per cent adherence to acamprosate at month 6 and 95% CI for key comparisons (adjusted for baseline site, SADQ score and prescribed relapse medication)

	All participants	Followed up on time
CM vs. SS	–10.59 (–19.57; –1.62)	–12.77 (–22.10; –3.43)
MM vs. SS	–3.14 (–12.80; 6.51)	–3.94 (–14.08; 6.19)
CM vs. MM	–7.95 (–18.69; 2.79)	–9.19 (–20.37; 1.99)

**TABLE 13** Analysis by treatment allocated and CACE analysis by allocated group (per cent adherent to acamprosate at month 6)

	ATA	CACE
100% adherent		
CM vs. SS	-10.59 (-19.57; -1.62)*	-22.19 (-29.71; -14.66)*
MM vs. SS	-3.14 (-12.80; 6.51)	-31.78 (-60.46; -3.10)*
50% adherent		
CM vs. SS	-10.59 (-19.57; -1.62)*	-12.45 (-17.76; -7.14)*
MM vs. SS	-3.14 (-12.80; 6.51)	-13.2 (-25.38; -1.15)*
* $p < 0.05$ .		

Under scenario 1, 50% adherence, the mean difference in per cent adherence increases from 10.6% (95% CI 19.6% to 1.62%) to 12.45% (95% CI 17.8%) in the SS + MM + CM versus SS comparison. This indicated that at 50% compliance, those allocated to SS + MM + CM have a mean of 12.4% more adherence to acamprosate at month 6 than those allocated to SS alone. When comparing the SS + MM versus the SS group, a previous non-significant difference of 3.14% (95% CI 12.8% to -6.5%) becomes a significant difference of 13.2% (25.4% to 1.15%). Under scenario 2, the differences are larger in magnitude, the SS + MM + CM group having 22.2% (95% CI 29.7% to 14.7%) more adherent days than the SS group alone. While the magnitude of difference is larger for the SS + MM versus SS comparison 31.8% (95–60.5% vs. 3.10%), this comparison is based on a small number of participants ( $n = 20$ ), and should be interpreted with caution.

## Secondary outcome analysis

A similar analytical approach was employed to assess secondary outcomes. [Table 14](#) presents the distribution, mean and median of per cent days abstinent from alcohol at month 6 by allocated group and [Table 15](#) presents the ATA and CACE analysis, under scenario 2, for per cent days abstinent at month 6.

The ATA indicates lower per cent days abstinent at month 6 in the SS compared to both SS + MM + CM and SS + MM, but these are not significant; when compliance is incorporated, those who are 100% compliant have a significantly lower per cent days abstinent at month 6 in the SS group compared to both the SS + MM + CM and SS + MM groups.

Analysis of other secondary variables; per cent adherence to acamprosate at month 12, per cent days abstinent at month 12, standard drinks consumed, per cent days heavy drinking, drinks per drinking day, severity of alcohol dependence, alcohol urge, beliefs in medication and MMAS-8 showed no significant differences between the groups at either month 6 or 12 post randomisation. The results of these analyses are presented in [Appendix 1](#).

[Table 15](#) presents the results of a CACE analysis of compliance with MM and outcomes in terms of per cent days abstinent at month 6. Those who comply with MM are significantly more likely to have improved alcohol use outcomes, 12.5% more per cent days abstinent in the SS + MM + CM group and 15.1% more in the SS + MM group compared to SS alone, although the differences in the SS + MM group should be taken with caution considering the small numbers involved.

[Figure 2](#) presents error bars of median and interquartile range (IQR) of per cent days abstinent at month 6 categorised into first, second and third terciles. It is clear overall and for those still drinking

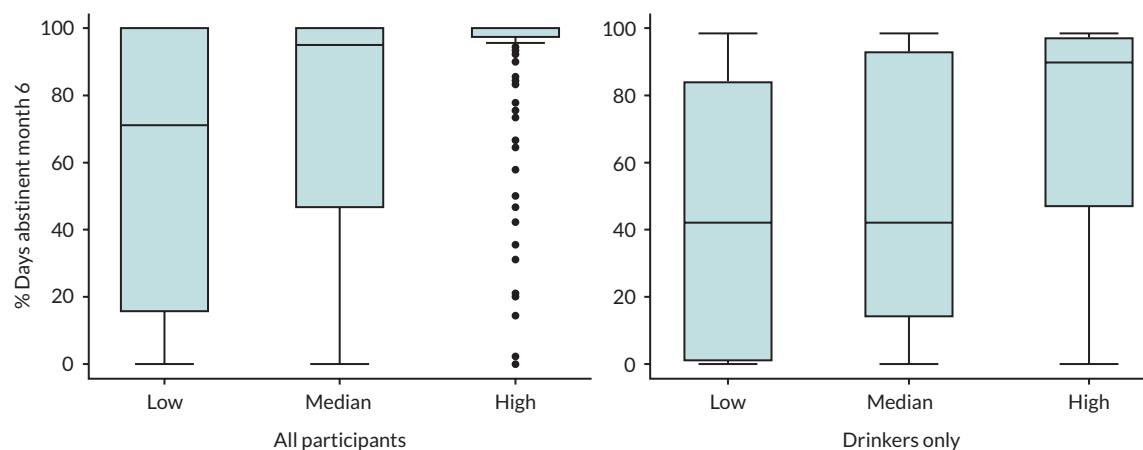
**TABLE 14** Mean (SD), median and distribution for per cent days abstinent at month 6 by allocated group

	SS + MM + CM (n = 139)	SS + MM (n = 119)	SS (n = 243)
Mean (SD)	74.1 (37.1)	72.4 (37.9)	69.6 (38.3)
Percentiles			
1%	0	0	0
5%	0	0	0
10%	0	0	0
25%	46.67	40	38.9
Median	97.78	97.78	94.4
75%	100	100	100
90%	100	100	100
95%	100	100	100
99%	100	100	100

**TABLE 15** Analysis by treatment allocated and CACE analysis by allocated group (per cent days abstinent at month 6)

	ATA	CACE
100% adherent		
CM vs. SS	-3.76 (-12.0; 4.50)	-12.5 (-21.1; -3.90)*
MM vs. SS	-4.40 (-11.9; 3.16)	-15.1 (-26.10; -4.20)*

\*  $p < 0.05$ .

**FIGURE 2** Median and IQR for per cent days abstinent at month 6 by tercile of adherence to acamprosate for all participants and those still drinking at month 6.

that there is an association between increased adherence to acamprosate and better drinking outcomes. A significant Spearman correlation coefficient of 0.3944 ( $p < 0.001$ ).

Stepwise regression was conducted to model the between pre-randomisation factors and per cent adherence to acamprosate and per cent days abstinent at month 6. Interaction terms with treatment allocation were included in the model and a significance level of 0.1 was used as a threshold to

determine which variables were maintained in the final model reported. Baseline variables included initially in the model include age, gender, marital status, ethnicity, current employment status, number of children, age of first drink, weekly and daily drinking, frequency and quantity of alcohol consumption, severity of alcohol dependence, alcohol urges and alcohol-related problems. This analysis was augmented with an additional analysis for the SS + MM and SS + MM + CM groups where the same dependent variable was assessed with the same independent variables with the addition of therapeutic alliance.

With the dependent variable per cent adherence to acamprosate at month 6, item reduction analysis indicated the following baseline independent variables should be included in the model: allocation, site, having children, age, age of first alcoholic drink, alcohol-related problems, affective and common domains and alcohol urges. The full model specification is presented in [Appendix 1, Table 25](#). SS alone predicted lower adherence, and lower alcohol urge predicted lower adherence; no other variables were significant prognostic indicators of outcome. With per cent days abstinent at month 6 as the baseline dependent variables included in the model were allocated arm, site, alcohol urge, per cent days abstinent and per cent days heavy drinking, only alcohol urges were significant with lower alcohol urges predicting lower per cent days abstinent at month 6. The full model specification is presented in [Appendix 1, Table 26](#). For the two intervention groups SS + MM and SS + MM + CM, the prognostic analysis was augmented with an analysis including a measure of therapeutic alliance, and therapeutic alliance did not predict per cent adherence to acamprosate at month 6 for either of the allocated groups.

## Summary of results

In sum, we set out to recruit 748 participants and allocate them in a ratio of 2 : 1 : 1 to SS, SS + MM and SS + MM + CM, respectively. To address our sample size requirements, we aimed to follow up 70% of these at the primary end point, 6 months post randomisation. We achieved this aim.

Our primary outcome was per cent adherence to acamprosate at month 6. When comparing SS + MM + CM versus SS alone, we observed a significantly higher per cent adherence to acamprosate in the SS + MM + CM group; the differences were of the magnitude that would indicate a clinically important difference. Differences were also observed when comparing SS + MM versus SS and SS + MM + CM versus SS + MM, but these were not significant. We explored how robust these findings were to assumptions about the nature of any missing data and we explored a missing data imputation model to explore the impact of data that may be MAR and a sensitivity analysis to explore data that may not be MAR. Neither of these analyses found any significant deviation from the analysis based on observed values, so we can be confident that our findings from the ATA analysis are robust. To explore the effect of compliance to MM, we conducted a CACE analysis using two scenarios of compliance, 50% and 100% compliance. In both scenarios, we found greater benefits associated with SS + MM + CM and SS + MM versus SS alone and these benefits were significant and clinically important.

Our secondary analysis included per cent days abstinent from alcohol at month 6. The ATA found differences favouring both intervention groups over SS alone but neither of these was significant. When a CACE analysis was conducted using scenario 2, both intervention groups had significantly greater per cent days abstinent than SS alone. This analysis also highlighted the relationship between adherence to acamprosate and better outcomes something additionally highlighted by a medium significant correlation between adherence to acamprosate and increased per cent days abstinent at month 6.

Our prognostic analysis found little evidence of baseline predictors for either adherence to medication or per cent days abstinent at month 6. There was no evidence that increased therapeutic alliance in the intervention groups was associated with increased adherence.



# Chapter 5 Health economic evaluation

## Methods

### *Method of economic evaluation*

The primary economic analysis was a cost-utility analysis where outcomes were expressed as QALYs, as recommended by NICE.<sup>129</sup> A secondary analysis explored cost-effectiveness in terms of the primary clinical outcome which was adherence to relapse prevention medication.

### *Perspective*

The primary economic perspective was the NHS and personal social services (NHS/PSS) perspective preferred by NICE. This covers all hospital, community health and social services. A sensitivity analysis based on a broader perspective including impact on the criminal justice sector was planned, however, this became redundant because criminal activity was not reported by any patient at any time point.

### *Time horizon*

The primary time horizon of the economic analyses using both QALYs and relapse medication adherence was the 6-month follow-up, consistent with the primary clinical analysis. A secondary analysis was carried out at the 12-month follow-up using QALYs.

### *Outcomes*

The primary economic outcome was QALYs calculated using the EQ-5D-5L measure of health-related quality-of-life scores at baseline, 6- and 12-month follow-ups. The EuroQol-5 Dimensions (EQ-5D) is a non-disease-specific measure for describing and valuing health-related quality of life.<sup>118</sup> The measure covers five health domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) which are rated on five levels (e.g. no, slight, moderate, severe, extreme problems).

The EQ-5D-5L (five levels) is a revised version of the EuroQol-5 Dimensions, three-level version (EQ-5D-3L). It has been established that the EQ-5D-3L can be used with confidence in economic evaluations for alcohol dependence.<sup>114</sup> The health states from the EQ-5D-5L were given a utility score using responses from a representative sample of adults in the UK.<sup>125</sup> These utility scores, however, have not been accepted by NICE which instead recommends using EQ-5D-3L values based on a cross-walk algorithm.<sup>126</sup> Accordingly, a cost-utility analysis based on the EQ-5D-3L values is presented as a sensitivity analysis.

### *Economic model*

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. Economic modelling can be utilised to project costs and QALYs beyond the trial end points. A de novo patient level, multistate life table model was built using published risk equations<sup>130</sup> to estimate the effects of changing alcohol consumption on costs and QALYs over a 20-year time horizon.

### *Measurement of resources*

#### **Intervention resource use**

The clinical contact centre hosted by Celsio/Lloyds pharmacy recorded the number of telephone calls and the number of vouchers earned for each study participant and these were used as the basis for the calculation of the total cost of the intervention.

### Use of all other health and social care services

Data on use of other health and social care services included in the study were collected using the AD-SUS, modified for application to alcohol-dependent populations.<sup>131</sup> Information about study participants' use of services was collected in interview with a researcher at baseline and at 6- and 12-month follow-up interviews. The AD-SUS asks participants to report the number and duration of contacts with a range of health and social care professionals. At baseline, participants were asked to report services used in the previous 6 months. At follow-up, participants were asked to report services used since their last interview.

### Crime

The AD-SUS was also used to collect information about crimes committed by and against (victims of crime) participants. Responses were recorded by type of crime.

### Productivity

Changes in productivity were not measured as it was expected that < 10% of detoxified dependent drinkers would be employed or able to return to work. However, 28% of the sample were in full or part-time employment at baseline. Accordingly, productivity gains from reduced absenteeism, presenteeism and unemployment may represent an important economic benefit from treatment that was not recorded.

### Valuation of resources

A unit cost was applied to each resource used to calculate the total cost of resources used by each study participant (summarised in [Table 16](#)). All unit costs are for the financial year 2018–19, uprated where necessary using the GDP deflator.<sup>137</sup>

### Intervention cost

#### Medication Management

The unit cost per session was estimated by dividing the clinical call centre budget from Celsio/Lloyds pharmacy for the study by the total number of scheduled sessions. The call centre budgeted for telephone costs per session, pharmacist time per session, set up costs (phone lines, standard operating procedures, data management), pharmacist training costs and management costs. On this basis, the total cost for the initial session of 45 minutes was £89, and for each follow-up session of 15 minutes, it was £30.

#### Contingency Management

In addition to MM, participants in the CM group received vouchers based on the number of sessions they attended. Participants were given vouchers at the 6-month follow-up interview according to a CM reward schedule based on completed sessions. The CM schedule was a £5 voucher per completed session plus a £10 bonus for completing 4 calls, £20 for completing 8 calls and £30 for completing 12 calls.

#### Hospital and community services

Unit costs for inpatient and outpatient hospital services, Accident & Emergency attendances and use of ambulance services were taken from estimates based on NHS Reference Costs contained in the Unit Costs of Health and Social Care.<sup>133</sup> For NHS primary care services, social workers and social services support workers, we used costs contained in the Unit Costs of Health and Social Care.<sup>133</sup> Self-help groups without paid involvement of health-care professionals, such as Alcoholics Anonymous and SMART recovery meetings, were not valued.

**TABLE 16** Unit costs of health and social care services

Item	Source	Unit cost
Intervention		
Initial session	Celsio/Lloyds Pharmacy	£89 per session
Follow-up sessions	Celsio/Lloyds Pharmacy	£30 per session
Voucher administration	Celsio/Lloyds Pharmacy	£10 per session
Vouchers	Celsio/Lloyds Pharmacy	£5 per voucher
Accommodation		
Staffed accommodation	Residential rehabilitation for people who misuse drugs/alcohol <sup>132</sup>	£1040 per week
Hospital services		
Alcohol admissions	Alcohol services <sup>133</sup>	£424 per bed-day
Inpatient ≥ 5 days	NHS reference costs <sup>133</sup>	£3053 per episode
Inpatient < 5 days	NHS reference costs <sup>133</sup>	£631 per episode
Outpatient	NHS reference costs <sup>133</sup>	£135 per attendance
Accident and emergency	NHS reference costs (NHS Reference Costs 2018–19)	£166 per attendance
Ambulance	NHS reference costs <sup>133</sup>	£125 per attendance
Community health and social care services		
Alcohol keyworker	Alcohol health worker <sup>133</sup>	£76 per contact hour <sup>a</sup>
Psychiatrist	Psychiatric consultant <sup>133</sup>	£336 per contact hour <sup>b</sup>
Psychologist	Agenda for Change Band 7 <sup>133</sup>	£180 per contact hour <sup>c</sup>
Nurse specialist	Agenda for Change Band 6 <sup>133</sup>	£84 per contact hour <sup>a</sup>
Counsellor	Alcohol health worker <sup>133</sup>	£76 per contact hour <sup>a</sup>
Structured day program	Local authority day care <sup>133</sup>	£38 per client attendance
Recovery groups	Not valued	Zero rated
Alcoholics Anonymous	Not valued	Zero rated
Self-help lines and apps	Based on cost reported by the Samaritans <sup>134</sup>	£4.24 per call
Pharmacist	Celsio/Lloyds Pharmacy	£75 per contact hour <sup>d</sup>
Psychiatric nurse	Agenda for Change Band 5 <sup>133</sup>	£92 per contact hour <sup>a</sup>
Community Mental Health Team	Mental health specialist team (Improving Access to Psychological Therapies (IAPT), adult and elderly) NHS reference costs <sup>133</sup>	£96 per client attendance
General practitioner	General practitioner <sup>133</sup>	£34 per visit
Practice nurse	Nurse (GP practice) <sup>133</sup>	£50 per contact hour <sup>e</sup>
District nurse	Assumed equivalent to practice nurse	£50 per contact hour <sup>e</sup>
Occupational therapist	Community occupational therapist <sup>133</sup>	£80 per contact hour <sup>f</sup>
Accommodation worker	Assumed equivalent to Social Work Assistant <sup>133</sup>	£33 per contact hour <sup>a</sup>

continued

**TABLE 16** Unit costs of health and social care services (*continued*)

Item	Source	Unit cost
Social worker	Social worker <sup>133</sup>	£255 per contact hour <sup>g</sup>
Day centre	Assumed equivalent to structured day program	£38 per client attendance
Advice service	Assumed equivalent to social work assistant <sup>133</sup>	£33 per contact hour <sup>a</sup>
Medications		
Acamprosate 333 mg	Drug Tariff (Part VIII) <sup>135</sup>	Pack of 168 tablets £37.70
Naltrexone 50 mg	Drug Tariff (Part VIII) <sup>135</sup>	Pack of 28 tablets £57.95
Nalmefene 18 mg	Drug Tariff (Part VIII) <sup>135</sup>	Pack of 14 tablets £42.42
Disulfiram 200 mg	Drug Tariff (Part VIII) <sup>135</sup>	Pack of 50 tablets £111.53

a Cost per contact hour calculated multiplying the cost per working hour by the ratio of direct to indirect time for each type of service reported in Curtis and Burns.<sup>133</sup>

b Ratio of direct to indirect time of 1 : 2.03 reported in Curtis and Burns.<sup>136</sup>

c Ratio of direct to indirect time of 1 : 2.33 reported in Curtis and Burns.<sup>136</sup>

d Ratio of direct to indirect time of 1 : 0.25 reported in Curtis and Burns.<sup>136</sup>

e Ratio of direct to indirect time of 1 : 0.18 reported in Curtis and Burns.<sup>136</sup>

f Ratio of direct to indirect time of 1 : 0.67 reported in Curtis and Burns.<sup>136</sup>

g Ratio of direct to indirect time of 1 : 4.0 reported in Curtis and Burns.<sup>136</sup>

### Alcohol relapse prevention medication

Medication costs were calculated using daily dose information, the cost of the generic drug and controlled drug dispensing costs as per the NHS Business Services Authority website.<sup>135</sup>

### Costs of crime

Participants did not report committing crimes at any time point. A small number of participants reported being victims of crime at the 6-month follow-up ( $n = 28$ , 5%) and the 12-month follow-up ( $n = 33$ , 8%) – these reports were evenly distributed across groups (see results for more detail). A secondary analysis taking a broader perspective for costs from the NHS/PSS based on these few data was considered to be uninformative, and, accordingly, victim of crime data are presented descriptively and are not valued.

### Data analysis

#### Resource use

Resource use by study participants is reported as the mean (SD) by group and as a percentage of the group who had at least one contact. Differences in the use of services between randomised groups are reported descriptively and are not compared statistically to avoid problems associated with multiple testing, and because the focus of the economic evaluation was on the quantitative analysis of cost and cost-effectiveness.

### Difference in costs and outcomes

We initially present the unadjusted observed data on costs and outcomes. We imputed missing cost and outcome data using multiple imputation using chained equations (MICE) under the assumption that these data were MAR.<sup>138</sup> Multiple imputation in the economic analysis included baseline costs and baseline utilities as covariates in the chained equations which led to slightly different imputed estimates to the clinical analysis. Multiple imputation indicates the sensitivity of results to missing data under the assumption that the data are MAR. It is generally accepted that multiple imputation provides less biased estimates of costs and effects than complete case analysis unless data are MNAR. Differences in the imputed data on

costs and outcomes were adjusted for baseline costs or outcomes, as relevant, and baseline stratification variables and covariates pre-specified in the statistical analysis plan [severity of alcohol dependence (SADQ score of  $\leq 30$  or  $> 30$ ), study site, prescription of other relapse prevention medication (yes/no) and gender].

### Cost-effectiveness and cost-utility analyses

The primary economic analysis was composed of two separate comparisons: (1) SS + MM + CM versus SS alone; and (2) SS + MM versus SS alone, both at 6 months post randomisation, and assessed cost-effectiveness in terms of cost per QALY using the EQ-5D measure of quality of life. QALYs were calculated using the area under the curve approach as defined by the utility values at baseline and each follow-up. It was assumed that changes in utility score over time followed a linear path.<sup>139</sup> Two secondary economic evaluations were carried out, a cost-utility analysis at 12 months post randomisation using QALYs as the measure of effect and a cost-effectiveness analysis using adherence to relapse medication which was the primary clinical outcome.

Initially, incremental cost-effectiveness ratios (ICERs) were calculated, which are the difference in mean cost divided by the difference in mean effect.<sup>140</sup> Repeat resampling (bootstrapping) from the cost and outcomes data was used to generate a distribution of mean costs and effects.<sup>141</sup> The probability that each of the two treatments, SS + MM + CM and SS + MM, were cost-effective compared to the comparison group, SS alone, was explored using cost-effectiveness acceptability curves (CEACs) which are graphical representations of the probability that one treatment is cost-effective compared to another for a range of possible levels of willingness to pay for unit improvements in outcome (in this case, either QALYs or adherence to medication).<sup>141</sup>

### Sensitivity analyses

Sensitivity analyses were carried out to test the impact of varying methods and assumptions on the relative cost-effectiveness of the interventions being compared. We planned three sensitivity analyses:

1. A broader analytical perspective to include the cost of crime (which was not completed as no crimes were reported).
2. A complete case analysis for comparison with the results that used multiple imputation for missing data.
3. A cost-utility analysis using QALYs calculated from EQ-5D-3L tariffs, currently the approach preferred by NICE.

### Economic model

The decision-analytic model methods, assumptions and parameter inputs are specified in the Project Webpage Document.

## Results

### Data completeness

Full service use data at the 6-month follow-up point were available for 76% (141/185) in the SS + MM + CM group, 67% (122/182) in the SS + MM group and 69% (255/372) in the SS alone group, which was 70% of the total number randomised. Full service use data for the 6 months prior to the 12-month follow-up were available for 56% (104/185) in the SS + MM + CM group, 53% (96/182) in the SS + MM group and 52% (193/372) in the SS alone group, which was 53% of the total number randomised.

### Resource use

Resource use reported over the periods from baseline to 6-month follow-up and from 6-month to 12-month follow-up is summarised in [Table 17](#).

**TABLE 17** Service use between baseline and the 6-month follow-up (complete case)

	SS + MM + CM		SS + MM		SS (TAU)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Baseline to 6-month follow-up	(n = 141)		(n = 122)		(n = 255)	
MM (sessions)	7.7 (4.8)	83.2	6.2 (4.3)	80.2	0.0 (0.0)	0.0
CM (vouchers)	9.2 (3.7)	98.2	0.0 (0.0)	0.0	0.0 (0.0)	0.0
Supported accommodation (weeks)	3.1 (20.1)	5.0	15.1 (47.4)	12.6	10.4 (39.2)	7.9
Alcohol inpatient (nights)	1.8 (9.6)	10.6	2.1 (9.3)	12.3	1.3 (6.2)	11.0
Other inpatient (nights)	1.2 (4.9)	17.7	0.4 (1.7)	9.8	0.8 (4.3)	9.8
Alcohol outpatient (appointments)	0.2 (1.0)	4.3	0.1 (0.4)	2.5	0.2 (0.9)	5.5
Other outpatient (appointments)	0.9 (1.6)	38.3	1.1 (2.3)	32.8	1.0 (3.2)	28.2
Accident and emergency (visits)	0.3 (0.6)	26.2	0.3 (0.6)	27.9	0.4 (0.8)	31.4
Ambulance (calls)	0.2 (0.5)	14.2	0.2 (0.5)	12.3	0.3 (0.8)	16.5
Alcohol keyworker (contact)	6.8 (17.3)	66.7	5.5 (8.0)	68.8	5.8 (11.8)	62.7
Psychiatrist (contact)	0.5 (2.2)	13.4	0.3 (0.9)	13.9	0.4 (1.9)	13.4
Psychologist (contact)	0.1 (0.6)	5.6	0.1 (0.5)	2.5	0.3 (2.0)	5.1
Nurse specialist (contact)	1.1 (5.4)	16.9	2.1 (7.0)	25.4	2.5 (8.8)	21.6
Counsellor (contact)	1.4 (4.4)	15.5	2.9 (6.9)	23.8	1.4 (4.3)	13.8
Structured day program (visits)	8.3 (21.9)	21.8	5.6 (16.2)	19.7	9.7 (27.9)	23.6
Recovery groups (meetings)	7.8 (15.3)	37.3	9.8 (17.5)	43.8	9.2 (19.9)	39.0
Alcoholics Anonymous (meetings)	6.5 (22.9)	18.3	6.8 (18.7)	29.5	5.7 (17.9)	23.6
Self-help telephone or app (calls)	4.7 (24.3)	5.6	5.2 (26.5)	9.0	8.0 (38.8)	9.8
Pharmacists (contact)	5.0 (10.7)	67.6	4.3 (5.7)	66.4	3.9 (6.5)	63.1
Mental health team (visits)	0.4 (2.3)	7.0	0.1 (0.3)	4.1	0.3 (1.6)	5.1
GP (visits)	3.3 (4.0)	73.9	3.0 (2.8)	79.5	2.8 (3.3)	76.8
Practice nurse (contact)	0.9 (1.6)	42.3	0.7 (1.1)	40.2	0.8 (1.8)	39.8
Acamprosate (days prescribed)	120.0 (71.0)	80.8	101.0 (75.0)	73.8	100.0 (75.0)	75.3
Naltrexone/disulfiram (days prescribed)	4.1 (24.0)	3.5	9.4 (37.0)	8.2	2.0 (18.2)	2.0
Criminal activity (offences)	0.0 (0.0)	0.0	0.0 (0.0)	0.0	0.0 (0.0)	0.0
Six-month to twelve-month follow-up	(n = 104)		(n = 96)		(n = 193)	
Supported accommodation (weeks)	9.1 (45.0)	4.8	14.5 (47.9)	11.6	8.5 (36.4)	7.3
Alcohol inpatient (nights)	2.7 (20.5)	10.7	0.5 (3.1)	7.3	1.2 (4.3)	10.9
Other inpatient (nights)	1.1 (6.2)	12.6	0.7 (3.5)	10.4	0.7 (2.9)	11.9
Alcohol outpatient (appointments)	0.0 (0.1)	1.0	0.0 (0.1)	1.0	0.0 (0.4)	2.0
Other outpatient (appointments)	0.8 (1.7)	31.1	1.9 (4.7)	47.9	1.1 (2.6)	32.2
Accident and emergency (visits)	0.4 (0.7)	27.2	0.4 (0.6)	27.2	0.4 (0.6)	28.1
Ambulance (calls)	0.2 (0.5)	16.5	0.3 (0.8)	17.7	0.3 (0.6)	21.8
Alcohol keyworker (contact)	3.5 (10.4)	46.6	3.0 (6.0)	42.1	3.8 (7.2)	46.1

**TABLE 17** Service use between baseline and the 6-month follow-up (complete case) (*continued*)

	SS + MM + CM		SS + MM		SS (TAU)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Baseline to 6-month follow-up	(n = 141)		(n = 122)		(n = 255)	
Psychiatrist (contact)	0.4 (1.6)	14.4	0.3 (0.9)	11.5	0.3 (1.8)	7.8
Psychologist (contact)	0.2 (1.1)	4.9	0.1 (0.3)	3.1	0.3 (1.6)	4.1
Nurse specialist (contact)	0.2 (0.7)	10.8	0.3 (1.2)	8.3	0.5 (2.5)	13.0
Counsellor (contact)	0.9 (3.7)	8.4	2.6 (6.3)	20.9	1.1 (3.5)	12.9
Structured day program (visits)	2.5 (11.2)	7.4	0.1 (1.2)	1.2	2.7 (12.8)	8.8
Recovery groups (meetings)	3.8 (11.9)	22.3	3.6 (10.7)	22.9	4.7 (13.3)	28.5
Alcoholics Anonymous (meetings)	6.1 (22.5)	20.7	5.1 (15.5)	22.9	6.7 (31.6)	16.7
Self-help telephone or app (calls)	0.9 (7.5)	2.9	5.2 (27.2)	5.3	5.7 (32.4)	10.9
Pharmacists (contact)	3.1 (6.2)	46.6	3.1 (6.5)	42.7	2.8 (4.1)	50.8
Mental health team (visits)	0.4 (2.4)	5.8	0.1 (0.7)	3.1	0.6 (3.9)	9.3
GP (visits)	2.1 (2.9)	64.1	3.1 (4.3)	71.6	2.7 (4.0)	74.1
Practice nurse (contact)	0.7 (1.8)	29.2	1.0 (3.0)	37.5	1.0 (2.3)	45.1
Acamprosate (days prescribed)	43.6 (74.0)	26.0	36.8 (69.8)	21.9	47.0 (75.6)	28.0
Naltrexone/disulfiram (days prescribed)	3.2 (23.2)	2.0	6.7 (30.5)	6.3	1.7 (17.1)	1.0
Criminal activity (offences)	0.0 (0.0)	0.0	0.0 (0.0)	0.0	0.0 (0.0)	0.0

### Interventions

Patients in the SS + MM + CM group attended more MM sessions than the SS + MM group (mean 7.7 sessions per participant vs. 6.1). Patients in the SS + MM + CM group received an average of around nine vouchers out of a possible 12; 98% received at least one voucher.

### Health and social care services

Apart from less reported use of supported accommodation in the SS + MM + CM group (mean 3.1 weeks per participant) compared to the SS + MM group (mean 15.1 weeks) and the SS group (mean 10.4 weeks) over the 6-month follow-up, the use of other health and social care services was broadly similar across the three randomised groups over this period.

Over the period from the 6-month to the 12-month follow-up, the use of supported accommodation was highest in the SS + MM group (mean 14.5 weeks per participant), compared to the SS + MM + CM group (mean 9.1 weeks) and the SS group (mean 8.5 weeks). The use of all other health and social care services was broadly comparable across all three groups.

### Alcohol relapse prevention medication

The SS + MM + CM group were prescribed acamprosate for a longer period on average (mean 120 days) compared to the SS + MM group (mean 101 days) and the SS group (mean 100 days) over the 6-month follow-up period. The pattern remained similar when including use of other relapse medication, with the highest use in the SS + MM + CM (mean 124 days) compared to the SS + MM group (mean 110 days) and the SS group (mean 102 days). Over the 6- to 12-month follow-up period, the SS group were prescribed acamprosate for a longer period on average (mean 47 days) compared to the SS + MM + CM group (mean 44 days) and the SS + MM group (mean 37 days). However, these differences reduced when all relapse medications were combined (mean 49 days SS; 47 SS + MM + CM; 44 SS + MM).

## Crime

Participants did not report committing any criminal offences over the 6-month or 12-month follow-up periods. This is consistent with data suggesting that most alcohol-related crimes, such as assault and domestic abuse, are due to alcohol abuse rather than alcohol dependence.<sup>142</sup> At 6 months, 28 (5%) of participants followed up (SS + MM + CM  $n = 5$  (4%), SS + MM  $n = 8$  (7%), SS  $n = 15$  (6%)) reported being victims of crime including fraud ( $n = 2$ ), personal theft ( $n = 7$ ), house burglary ( $n = 4$ ), criminal damage ( $n = 1$ ), assault ( $n = 9$ ), harassment ( $n = 4$ ) and domestic violence ( $n = 1$ ). At 12 months, 33 (8%) of participants followed up [SS + MM + CM  $n = 9$  (9%), SS + MM  $n = 10$  (10%) SS  $n = 14$  (7%)] reported being victims of crime including fraud ( $n = 2$ ), personal theft ( $n = 6$ ), house burglary ( $n = 6$ ), criminal damage ( $n = 2$ ), assault ( $n = 9$ ), harassment ( $n = 5$ ) and indecent assault ( $n = 3$ ).

## Costs

### Disaggregated costs

[Table 18](#) summarises health and social care costs from the NHS/PSS perspective over the baseline to 6-month and 6-month to 12-month follow-up periods. Disaggregated costs are based on complete case data as data imputation was conducted at the aggregate level. Over the baseline to 6-month follow-up period, the SS + MM + CM group had the lowest total costs per participant (mean £3628), due primarily to lower supported accommodation costs. The SS + MM group had the highest costs (mean £5068), due to higher costs in supported accommodation. For the 6-month to 12-month follow-up period, cost differences between the groups were smaller, with the SS + MM + CM group having the lowest total costs (mean £2926) and the SS + MM having the highest costs (mean £3721). In total, over the full period from baseline to 12-month follow-up, total costs were similar for the SS + MM + CM group (mean £6372) and the SS group (mean £6258) but were higher in the SS + MM group (mean £8264).

### Differences in costs

The results of tests of differences in imputed and adjusted health and social care costs from the NHS/PSS perspective at the primary 6-month follow-up and the secondary 12-month follow-up are presented in [Table 19](#). The SS + MM + CM group was £467 less costly on average than SS over the baseline to 6-month follow-up period but £276 more costly over the full follow-up period from baseline to 12-month follow-up. The SS + MM group was £380 more costly on average than SS over the 6-month follow-up period and £362 more costly over the full 12-month follow-up period. Differences in costs were not statistically significant at any follow-up time point.

### Primary cost-utility analysis

#### EQ-5D-5L scores

EQ-5D-5L health states are summarised in [Figure 3](#) based on the complete data. The graph shows that the average health state values at baseline were similar for all groups (range 0.786–0.809). At the 6-month follow-up point, the average health state values were also similar for all groups (range 0.778–0.805), although with small declines seen in the SS + MM + CM and SS groups. At the 12-month follow-up, the SS + MM + CM and SS + MM treatment groups recorded small gains compared to baseline of + 0.044 and + 0.026, respectively, while the SS group recorded a slight decline (–0.014).

#### QALYs

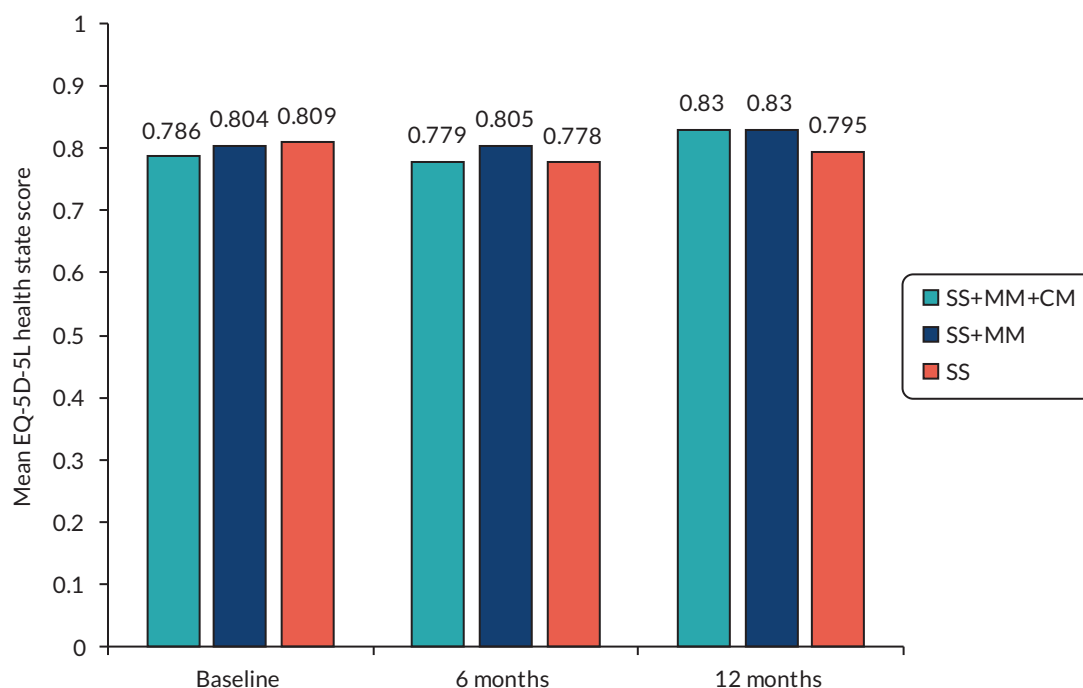
The results of tests on differences in imputed and adjusted QALYs at the primary 6-month follow-up and the secondary 12-month follow-up are presented in [Table 20](#). Differences between groups at the 6-month follow-up were small, with patients in the SS + MM + CM and SS + MM groups on average having slightly more QALYs than patients in the SS group, but these differences were not statistically significant. However, differences between groups were greater at the 12-month follow-up and were statistically significant for SS + MM versus SS (mean diff 0.015;  $p = 0.032$ ), but not for SS + MM + CM versus SS (mean diff 0.023;  $p = 0.151$ ).

TABLE 18 Disaggregated mean costs (£) (complete case)

	Baseline (previous 6 months)				Baseline to 6-month follow-up				Baseline to 12-month follow-up			
	SS + MM + CM (n = 185)	SS + MM (n = 182)	SS (TAU) (n = 372)	Mean (SD)	SS + MM + CM (n = 104)	SS + MM (n = 96)	SS (TAU) (n = 193)	Mean (SD)	SS + MM + CM (n = 104)	SS + MM (n = 96)	SS (TAU) (n = 193)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	Mean (SD)	
MM	0 (0)	0 (0)	0 (0)	0 (0)	280 (162)	233 (145)	0 (0)	0 (0)	280 (162)	233 (145)	0 (0)	0 (0)
CM vouchers	0 (0)	0 (0)	0 (0)	0 (0)	67 (50)	0 (0)	0 (0)	0 (0)	67 (50)	0 (0)	0 (0)	0 (0)
Acamprosate	0 (0)	0 (0)	0 (0)	0 (0)	162 (96)	137 (102)	135 (101)	198 (203)	221 (196)	187 (196)	198 (203)	198 (203)
Naltrexone/disulfiram	0 (0)	0 (0)	0 (0)	0 (0)	9 (52)	21 (81)	5 (40)	9 (78)	16 (100)	36 (149)	9 (78)	9 (78)
Supported accommodation	755 (3825)	2170 (10086)	1451 (5191)	453 (2991)	2246 (7035)	1542 (5828)	4094 (12096)	2044 (8984)	1533 (6849)	1287 (4601)	1098 (2327)	1098 (2327)
Hospital-based alcohol services	2123 (2195)	1908 (2385)	2156 (3328)	880 (4103)	968 (3957)	306 (725)	875 (1539)	596 (1409)	1321 (4719)	699 (1190)	1157 (1392)	1157 (1392)
Hospital-based other services	496 (1046)	485 (1231)	608 (1444)	486 (1019)	794 (1121)	981 (1584)	1327 (1738)	1591 (2331)	875 (1539)	699 (1190)	1157 (1392)	1157 (1392)
Community-based alcohol services	1214 (1755)	1069 (1259)	1009 (1116)	860 (1432)	363 (598)	375 (765)	732 (1310)	722 (1331)	1327 (1738)	571 (778)	8264 (13661)	8264 (13661)
Community-based other services	522 (901)	430 (674)	509 (1189)	431 (923)	5068 (8397)	4082 (7008)	6372 (10841)	6258 (10399)	732 (1310)	571 (778)	8264 (13661)	8264 (13661)
Total costs	5110 (5352)	6062 (10672)	5733 (7454)	3628 (7384)	5068 (8397)	4082 (7008)	6372 (10841)	6258 (10399)	6372 (10841)	8264 (13661)	6258 (10399)	6258 (10399)

**TABLE 19** Differences in imputed and adjusted costs

Costs	SS + MM + CM vs. SS			SS + MM vs. SS		
	Mean diff (SE)	95% CI	p	Mean diff (SE)	95% CI	p
Baseline to 6 months (£)	-467 (717)	-1874 to 941	0.515	380 (366)	-338 to 1098	0.299
Baseline to 12 months (£)	276 (1144)	-1976 to 2527	0.810	362 (552)	-722 to 1446	0.512

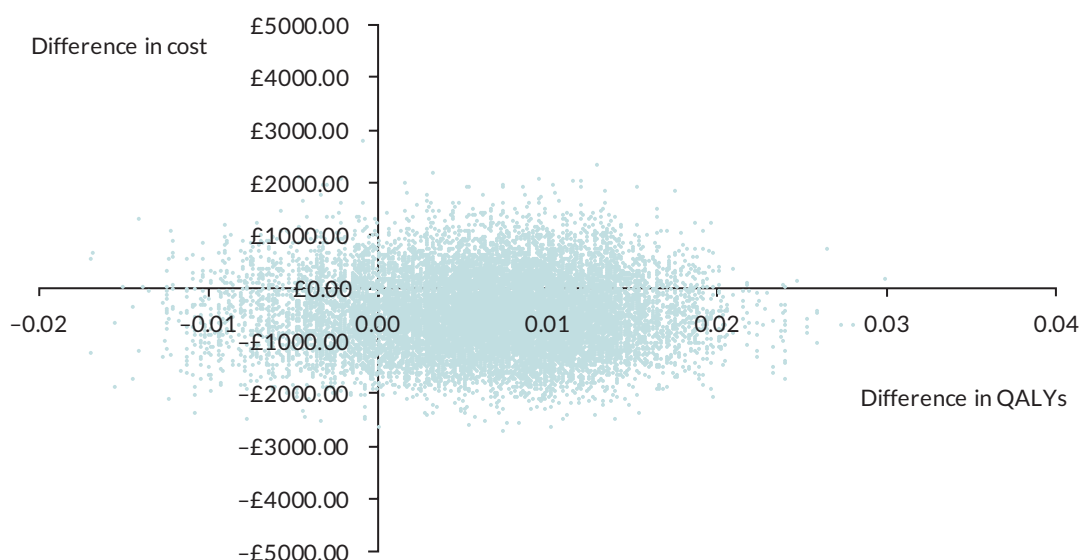
**FIGURE 3** Mean EQ-5D-5L health state scores over time by group.**TABLE 20** Differences in imputed and adjusted QALYs

Follow-up	SS + MM + CM vs. SS			SS + MM vs. SS		
	Mean diff (SE)	95% CI	p	Mean diff (SE)	95% CI	p
6 months	0.005 (0.005)	-0.006 to 0.015	0.384	0.004 (0.003)	-0.001 to 0.010	0.125
12 months	0.029 (0.017)	-0.006 to 0.063	0.102	0.015 (0.009)	0.001 to 0.032	0.032

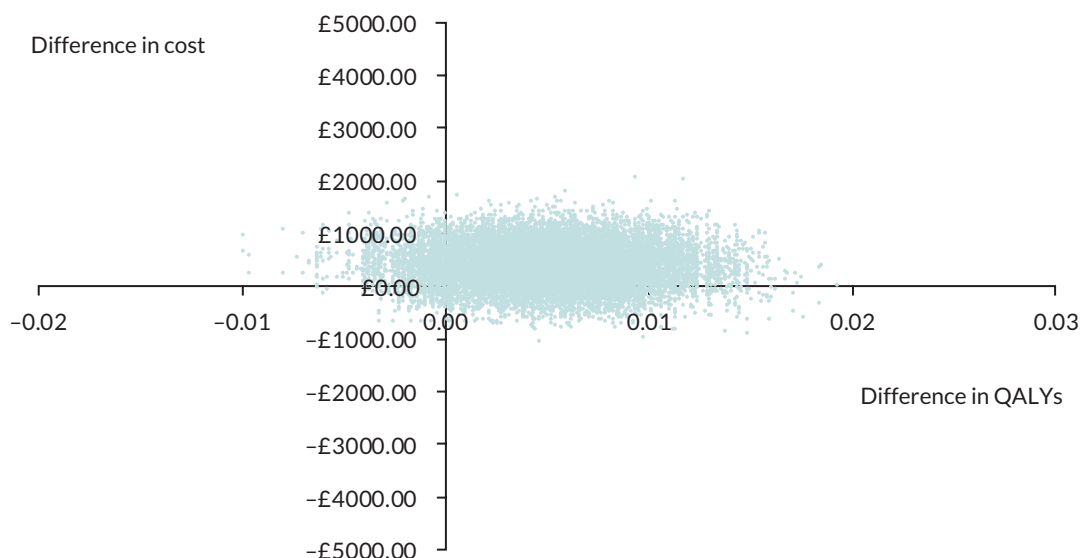
### Cost-utility analysis at 6-month follow-up

In the primary economic evaluation, a cost-utility analysis at the 6-month follow-up point, the SS + MM + CM group achieved small gains in QALYs compared to the SS group at a lower cost per participant. Thus, the SS + MM + CM group dominated the SS group (better outcomes, lower costs). The SS + MM group also achieved small gains in QALYs but at an additional cost per participant compared to the SS group. The ICER (additional cost per additional QALY) for the SS + MM group was £95,000 per QALY, which is well above the NICE £20,000–30,000 per QALY threshold.

The scatterplots in the cost-effectiveness planes in [Figures 4](#) and [5](#) illustrate uncertainty in the joint distribution of costs and outcomes generated using non-parametric bootstrap methods for SS + MM + CM versus SS and SS + MM versus SS, respectively, at the 6-month follow-up point. For SS + MM + CM (see [Figure 4](#)), the scatterplot illustrates that for the majority of replications, total costs were lower and total QALYs were higher for SS + MM + CM than SS. For SS + MM (see [Figure 5](#)),



**FIGURE 4** Scatterplot showing the bootstrapped mean differences in imputed costs and imputed QALYs for SS + MM + CM compared to SS at 6 months.



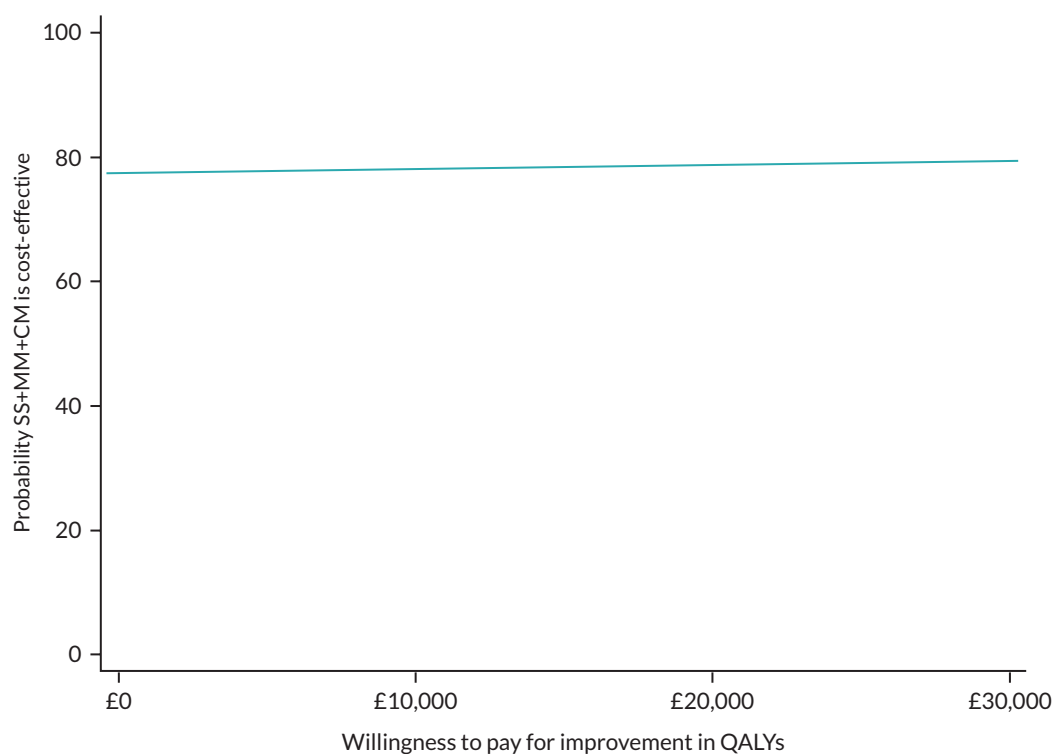
**FIGURE 5** Scatterplot showing the bootstrapped mean differences in imputed costs and imputed QALYs for SS + MM compared to SS at 6 months.

the scatterplot illustrates that for the majority of replications, total costs and QALYs were higher for SS + MM when compared to SS.

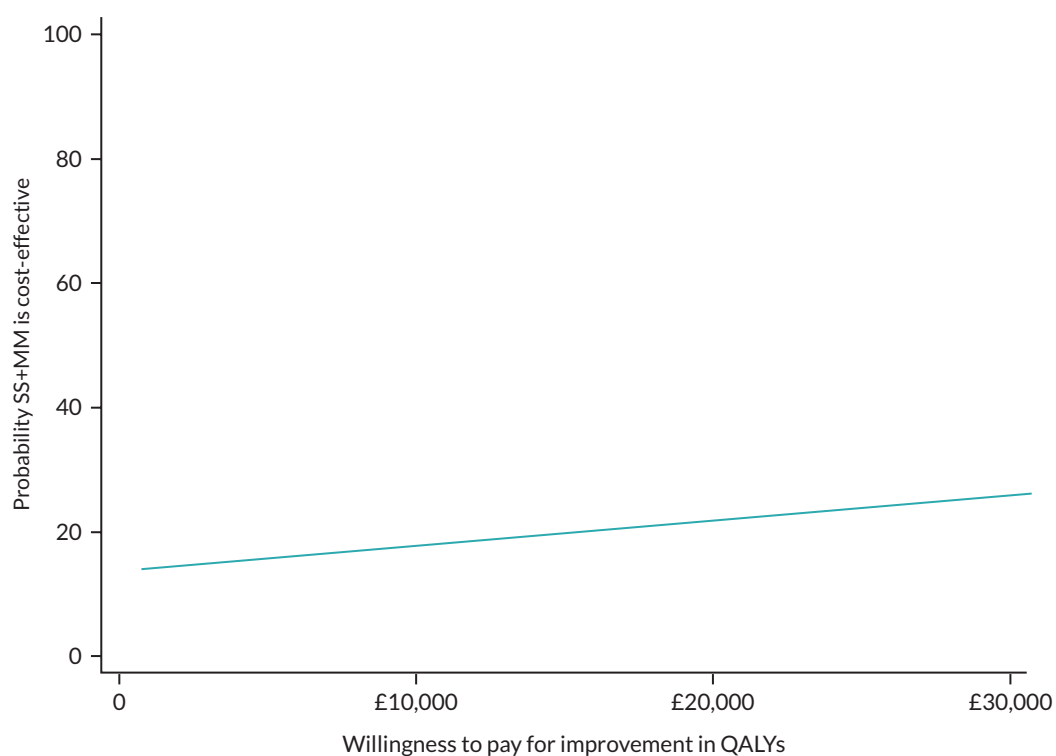
The CEAC in [Figure 6](#) shows that there was a 78% to 80% probability that SS + MM + CM was cost-effective compared to SS, using the NICE willingness-to-pay thresholds of £20,000–30,000 per QALY at the 6-month follow-up point. The CEAC in [Figure 7](#) shows that there was a 22% to 27% probability that SS + MM was cost-effective compared to SS, using the NICE willingness-to-pay thresholds of £20,000–30,000 per QALY at the 6-month follow-up point.

### Secondary cost-utility analysis at 12 months

At the secondary 12-month follow-up point, the SS + MM + CM group made gains in QALYs but at a higher cost per participant compared to the SS group. The ICER (additional cost per additional QALY) was £9517 per QALY, which is below the NICE £20,000–30,000 per QALY threshold. The SS + MM



**FIGURE 6** Cost-effectiveness acceptability curve showing the probability that SS + MM + CM is cost-effective compared to SS alone in terms of QALYs at 6 months.



**FIGURE 7** Cost-effectiveness acceptability curve showing the probability that SS + MM is cost-effective compared to SS alone in terms of QALYs at 6 months.

group also achieved gains in QALYs with an additional cost per participant compared to the SS group. The ICER (additional cost per additional QALY) for the SS + MM group compared to the SS group was £24,133 per QALY, also below the NICE threshold.

For SS + MM + CM, the 12-month scatterplot (see [Figure 8](#)) illustrates that in the majority of replications, total costs were greater and QALYs also greater compared to SS. For SS + MM, the 12-month scatterplot (see [Figure 9](#)) is similar to the SS + MM + CM versus SS comparison, with the majority of replications also showing higher costs and QALYs for SS + MM compared to SS.

The CEAC in [Figure 10](#) shows that the probability that SS + MM + CM was cost-effective compared to SS ranged between 61% and 68% using the NICE willingness-to-pay threshold of £20,000–30,000 per QALY. The CEAC in [Figure 11](#) shows that the probability that SS + MM was cost-effective compared to SS ranged between 48% and 581%, using the same thresholds.

### Secondary cost-effectiveness analysis at 6 months

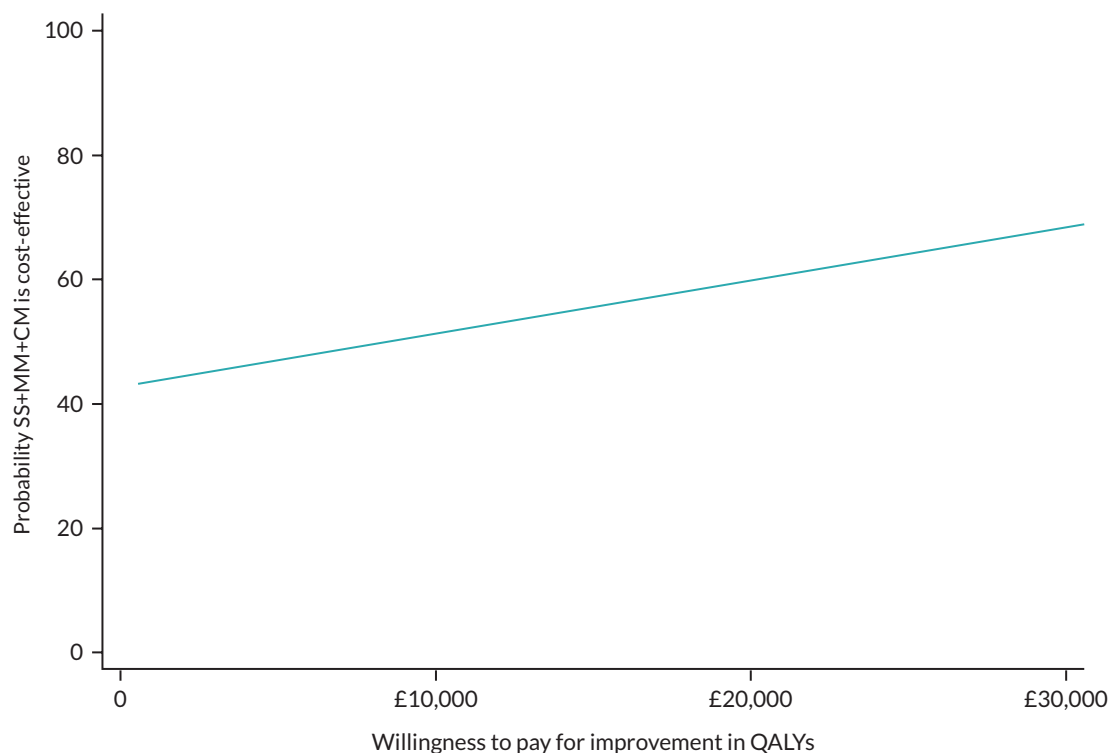
The primary clinical outcome was adherence to acamprosate medication expressed as percentage of days adherent at the 6-month follow-up. Adherence was highest in the SS + MM + CC group (47%,  $n = 141$ ), followed by SS + MM group (41%,  $n = 122$ ) and lowest in the SS group (38%,  $n = 255$ ).



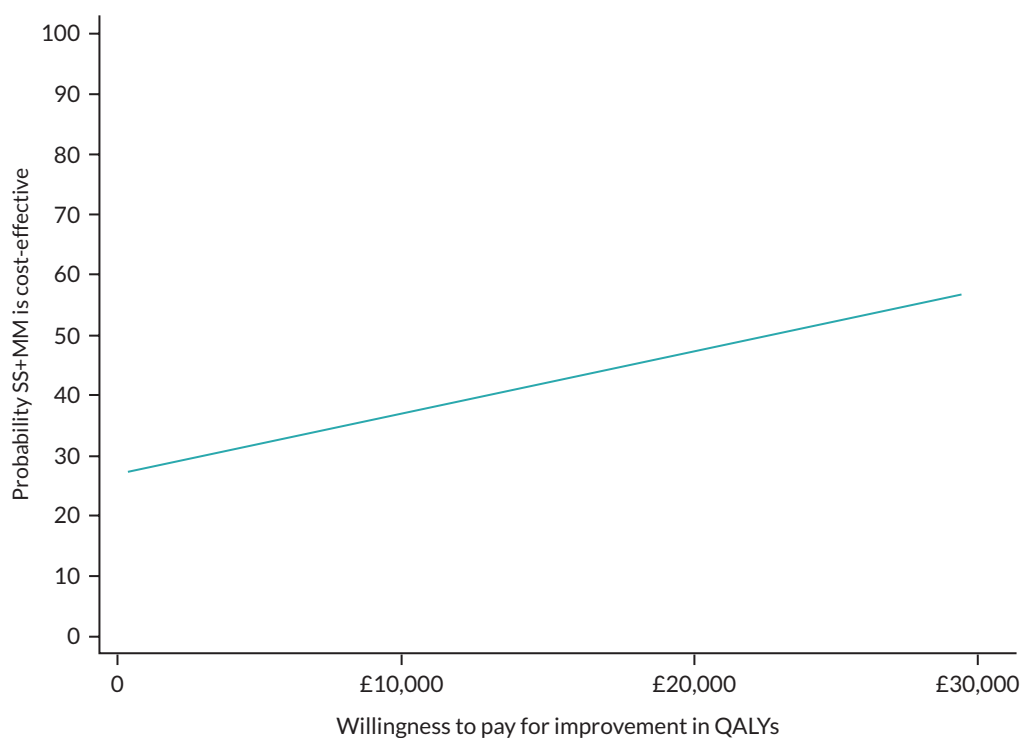
**FIGURE 8** Scatterplot showing the bootstrapped mean differences in imputed costs and imputed QALYs for SS + MM + CM compared to SS at 12 months.



**FIGURE 9** Scatterplot showing the bootstrapped mean differences in imputed costs and imputed QALYs of SS + MM compared to SS at 12 months.



**FIGURE 10** Cost-effectiveness acceptability curve showing the probability that SS + MM + CM is cost-effective compared to SS alone in terms of QALYs at 12 months.

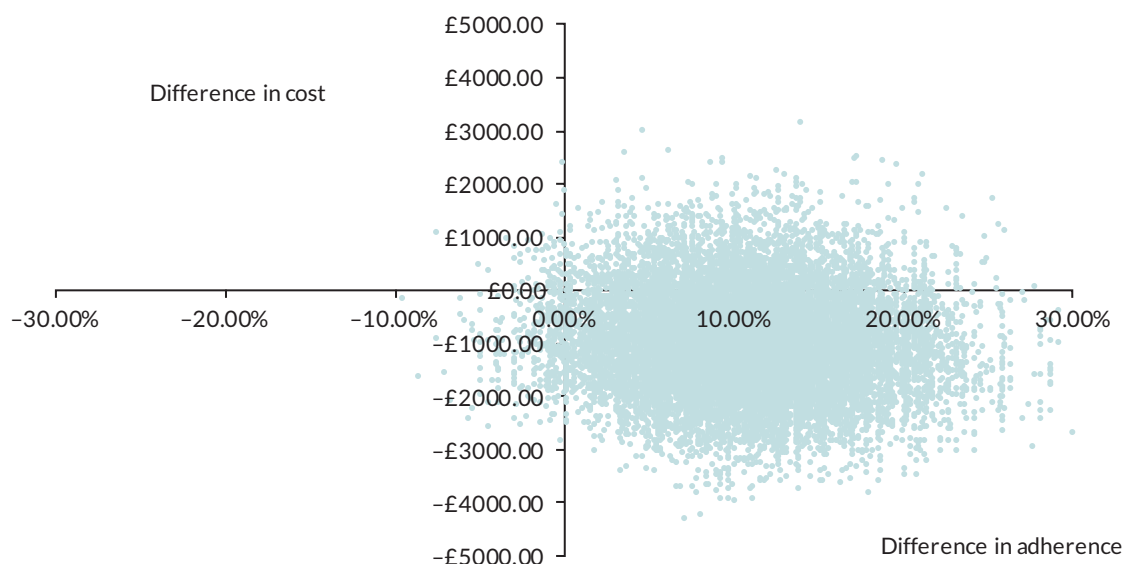


**FIGURE 11** Cost-effectiveness acceptability curve showing the probability that SS + MM is cost-effective compared to SS alone in terms of QALYs at 12 months.

The results of tests of differences in imputed and adjusted percentage of adherent days at the 6-month primary clinical follow-up point are presented in [Table 21](#). Note that multiple imputation in the economic analysis included baseline costs and baseline utilities as covariates in the chained equations leading to slightly different imputed estimates to the clinical analysis. Adherence was

**TABLE 21** Imputed and adjusted incremental medication adherence at 6 months

Outcome	SS + MM + CM vs. SS			SS + MM vs. SS		
	Mean diff (SE)	95% CI	p	Mean diff (SE)	95% CI	p
Adherence (%)	10.39 (4.52)	1.52 to 19.27	0.022	1.84 (2.32)	-2.72 to 6.41	0.428

**FIGURE 12** Scatterplot showing the bootstrapped mean differences in imputed costs and imputed medication adherence for SS + MM + CM compared to SS at 6 months.

better in both treatment groups compared to control, reaching statistical significance in the SS + MM + CM group.

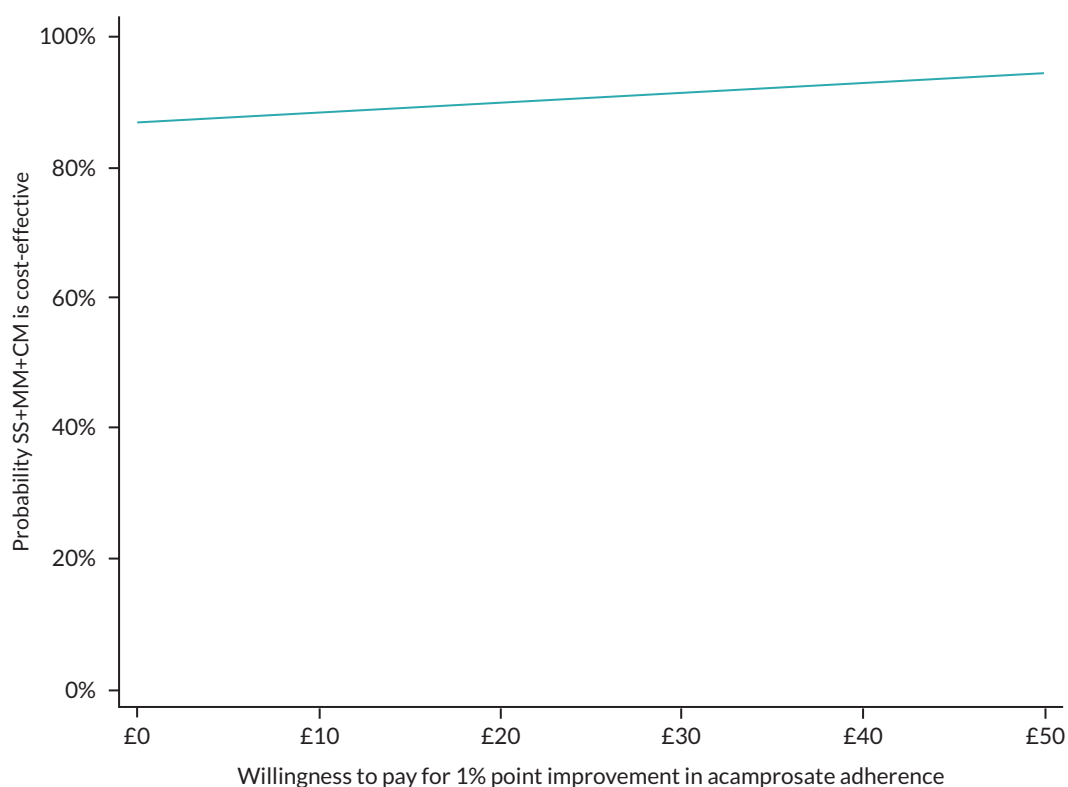
In terms of the primary clinical outcome at 6-month follow-up (acamprosate medication adherence), costs were lower and outcomes significantly better in the SS + MM + CM group compared to the SS group, so SS + MM + CM again dominated SS alone. For the SS + MM group, outcomes were better but costs were higher compared to the SS group, meaning that assessment of cost-effectiveness depends upon the maximum threshold value decision-makers would be prepared to pay for a unit change in outcome.

The scatterplots in the cost-effectiveness planes in [Figures 12](#) and [13](#) illustrate uncertainty in the joint distribution of costs and outcomes generated using non-parametric bootstrap methods, for SS + MM + CM versus SS and SS + MM versus SS, respectively. For SS + MM + CM (see [Figure 12](#)), the scatterplot clearly illustrates that for the majority of replications, total costs are lower for SS + MM + CM versus SS and effectiveness is higher. For the SS + MM group (see [Figure 13](#)), most replications fall in the north-east quadrant where both costs and effects are higher compared to the SS group.

The CEAC in [Figure 14](#) shows that the probability that SS + M + CM is cost-effective compared to SS is between 89% and 95% when decision-makers are willing to pay between £0 and £50 per percentage point improvement in medication adherence over 6 months. However, the probability that SS + MM is cost-effective compared to SS was only 18% to 22% across the same range of willingness-to-pay values (see [Figure 15](#)).



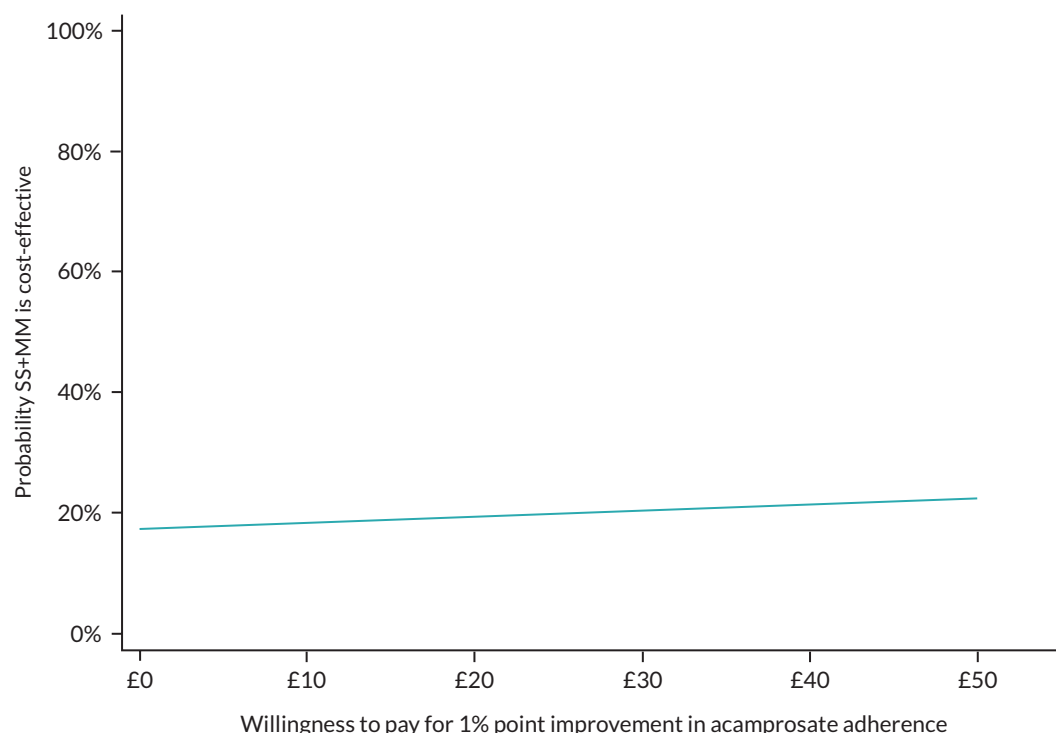
**FIGURE 13** Scatterplot showing the bootstrapped mean differences in imputed costs and imputed medication adherence for SS + MM compared to SS at 6 months.



**FIGURE 14** Cost-effectiveness acceptability curve showing probability that SS + MM + CM is cost-effective compared to SS in terms of acamprosate adherence at 6 months.

### Sensitivity analysis

Results of the sensitivity analyses are reported in [Table 22](#). Both the complete case analysis (rather than imputation of missing data) and the analysis using the EQ-5D-3L value set (rather than the EQ-5D-5L) produced similar results to the primary analysis at 6-month follow-up, indicating that the results of the primary analysis were robust to variation of assumptions.



**FIGURE 15** Cost-effectiveness acceptability curve showing the probability that SS + MM is cost-effective compared to SS in terms of acamprosate adherence at 6 months.

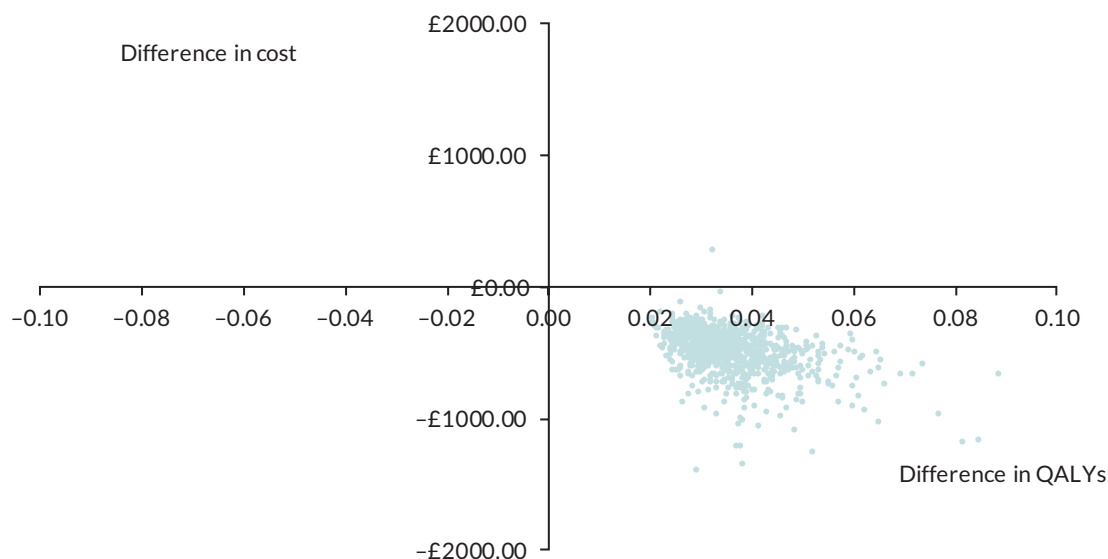
**TABLE 22** Sensitivity analyses

	SS + MM + CM vs. SS			SS + MM vs. SS		
	Mean difference in costs (£)	Mean difference in QALYs	ICER (cost per QALY)	Mean difference in costs (£)	Mean difference in QALYs	ICER (cost per QALY)
Primary analysis	-467	0.005	Dominant	380	0.004	£95,000
Complete case	-752	0.004	Dominant	295	0.003	£98,333
EQ-5D-3L	-467	0.004	Dominant	380	0.006	£63,000

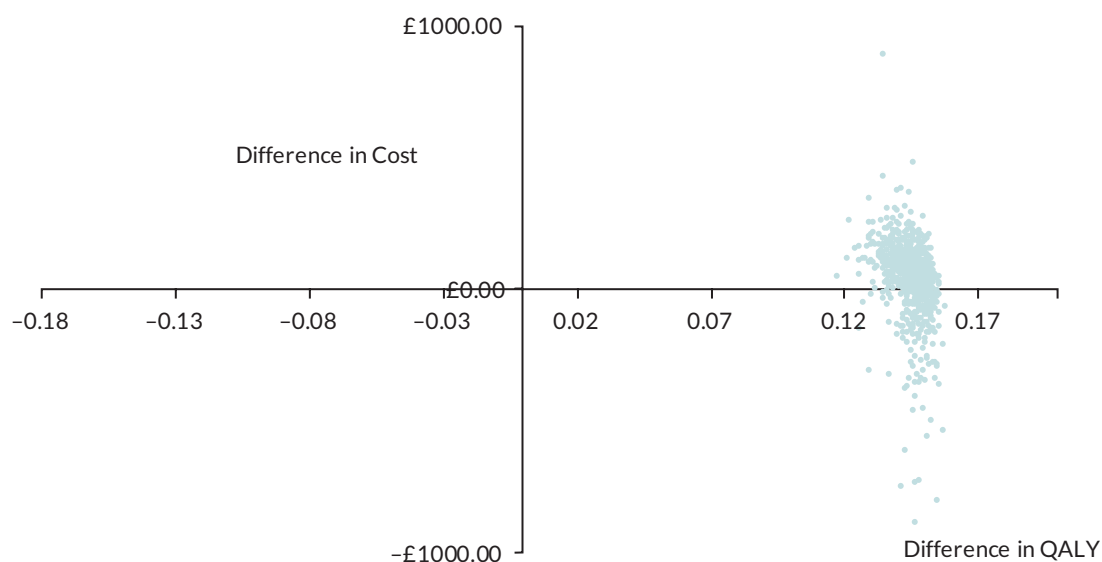
### Cost-effectiveness outcomes modelled over 20 years

Running the patient-level, multistate life table model over 20 years after the end of the trial produced results in favour of both SS + MM + CM and SS + MM compared to SS alone. The SS + MM + CM group dominated SS achieving 0.03 more discounted QALYs at a lower discounted cost of -£401 per participant. The SS + MM group achieved QALY gains of 0.15 discounted QALYs but at a higher discounted cost of £64 per participant compared to the SS group. The ICER (additional cost per additional QALY) was £427 per QALY, well below the NICE £20,000–30,000 threshold.

Probabilistic sensitivity analysis was used to vary model key parameters to estimate model uncertainty. For SS + MM + CM, the 20-year scatterplot (see [Figure 16](#)) shows that 999 out of 1000 simulations fell in the south-east quadrant, indicating more QALY gains at lower cost compared to SS. For SS + MM, the 20-year scatterplot (see [Figure 17](#)) shows relatively greater gains in QALYs compared to SS but with over half of these at a higher cost.



**FIGURE 16** Scatterplot showing the bootstrapped mean differences in imputed costs and imputed QALYs for SS + MM + CM compared to SS modelled over 20 years.



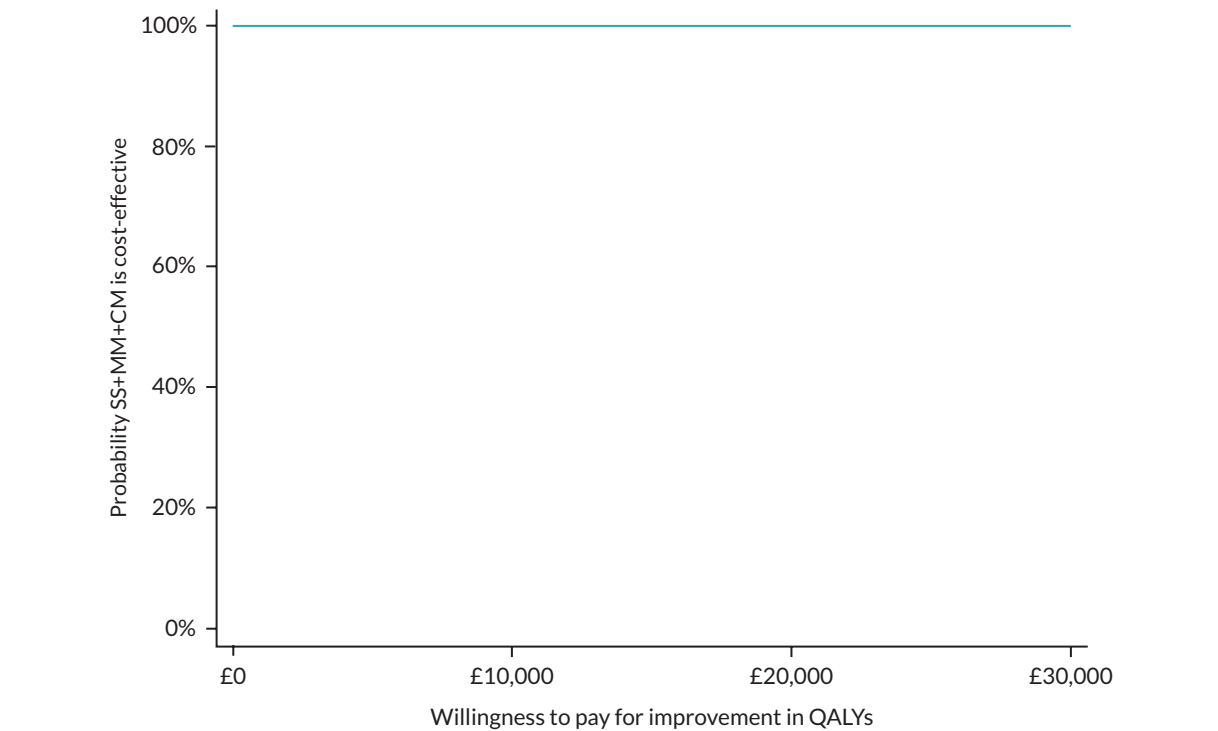
**FIGURE 17** Scatterplot showing the bootstrapped mean differences in imputed costs and imputed QALYs for SS + MM compared to SS modelled over 20 years.

The CEAC in [Figure 18](#) shows that the probability that SS + MM + CM was cost-effective compared to SS was 100% across all values of the NICE willingness-to-pay per QALY threshold plotted (£0–30,000). The CEAC in [Figure 19](#) shows that the probability that SS + MM was cost-effective compared to SS was 100% across the range of the NICE willingness-to-pay threshold of £20,000–30,000 per QALY.

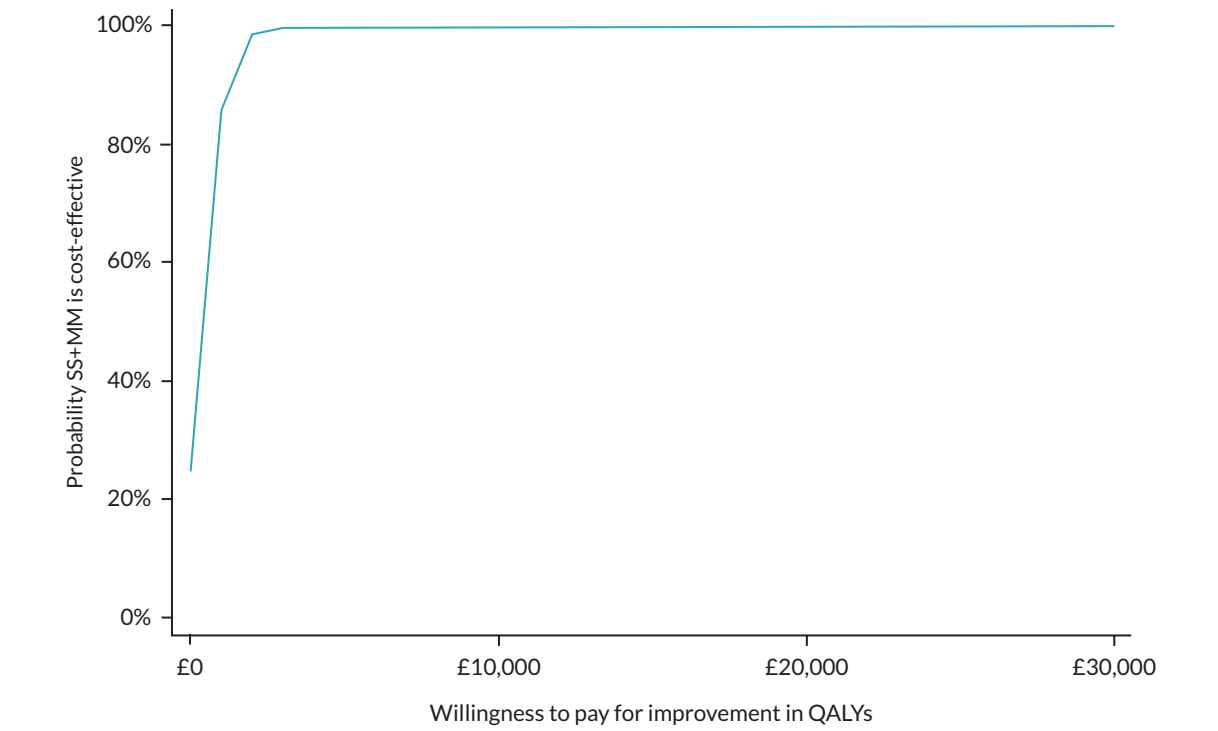
## Summary of findings

### SS + MM + CM versus SS

For SS + MM + CM versus SS, the primary economic analysis at 6-month follow-up using QALYs, the secondary economic analysis at 6-month follow-up using medication adherence and the economic modelling over a 20-year time horizon using QALYs all found SS + MM + CM to dominate SS (better outcomes at lower cost). At 12-month follow-up, although SS + MM + CM was not dominant, it



**FIGURE 18** Cost-effectiveness acceptability curve showing the probability that SS + MM + CM is cost-effective compared to SS in terms of QALYs modelled over 20 years.



**FIGURE 19** Cost-effectiveness acceptability curve showing the probability that SS + MM is cost-effective compared to SS in terms of QALYs modelled over 20 years.

generated more QALYs at an additional cost that was below the NICE cost per QALY threshold. There was, therefore, a higher probability of SS + MM + CM being cost-effective compared to SS alone in all analyses and at all time points.

***SS + MM versus SS***

For SS + MM versus SS, at 6- and 12-month follow-up and when modelled over 20 years, SS + MM achieved better outcomes at higher cost compared to SS. In terms of cost-effectiveness, SS + MM was not found to be cost-effective at 6-month follow-up but had a higher probability of being cost-effective compared to SS at both the 12-month follow-up (using the higher £30,000 per QALY NICE threshold) and when modelled over 20 years (over the full £20,000–30,000 cost per QALY threshold).

***Implications***

The results of the primary economic analysis at the 6-month follow-up point suggest that MM was only cost-effective when supported by voucher incentives to encourage support session uptake. This finding was heavily influenced by lower total costs in the SS + MM + CM group as a result of lower use of residential rehabilitation facilities compared to both SS + MM and SS alone, which may be related to the significantly higher medication adherence seen in the CM group. Over the medium (12 months) and longer term (20 years), SS + MM + CM remained cost-effective compared to SS and there was a higher probability of SS + MM being cost-effective compared to SS. These results support the addition of MM to SS for alcohol dependence, with or without CM. However, the economic benefit was stronger when CM was included.

## Chapter 6 Discussion

Contingency Management has an extensive evidence base showing effectiveness in the treatment of substance use disorder, but less was known about its application in the treatment of alcohol dependence.<sup>21,81</sup> There is greater evidence of CM reinforcing adherence to a range of interventions for substance use disorder, including medications, than for changes in consumption per se. However, there is evidence of effectiveness of CM targeted at reduced use of tobacco, cocaine, opiates and polysubstance use.<sup>143</sup>

Relapse prevention medications also have a strong evidence base, and acamprosate and naltrexone are recommended as first-line treatments for people with alcohol dependence in order to reduce the high relapse rate following initial detoxification.<sup>21</sup> However, despite the evidence of effectiveness from clinical trials, medication adherence is a common problem in clinical practice, with wide variation between trials, and adherence rates as low as 27% over 12 weeks in the only UK clinical trial of acamprosate.<sup>26,144</sup> There is also evidence from routine prescription data that many patients discontinue relapse prevention medication before the recommended 6-month course is completed; manufacturer's data suggest the average duration of acamprosate use is around 6 weeks. Both of these factors will limit the potential of this treatment to impact upon relapse, as poor medication adherence is associated with worse clinical outcomes. This led NICE to recommend further research on methods to increase medication adherence in alcohol dependence and on the potential of CM in alcohol dependence treatment more widely.<sup>21</sup>

We report here on a multicentre RCT of the effectiveness and cost-effectiveness of CM and another intervention, MM, to increase adherence to acamprosate in patients who have undergone detoxification from alcohol, in community addiction services in England. This was conducted and reported in accordance with international guidelines for research excellence.<sup>145</sup>

The MM intervention was adapted from the Medical Management intervention used to support medication adherence in a US NIH-funded Testing Combined Pharmacotherapies and Behavioral Interventions in Alcohol Dependence trial of naltrexone and acamprosate for alcohol dependence.<sup>44</sup> Medical Management was originally designed to be used by physicians in the Testing Combined Pharmacotherapies and Behavioral Interventions in Alcohol Dependence trial and subsequent studies.<sup>146-151</sup> However, we took advantage of recent developments in the UK of the extended clinical role of community pharmacists, including the HLP programme, which includes alcohol dependence as a key target population for pharmacist interventions.<sup>55,63,64,90,152</sup> We developed an effective partnership with Lloyds Pharmacy in order to implement a national pharmacist-delivered adaptation of the Medical Management intervention, known as MM. This was efficiently delivered by specially trained pharmacists from an established centralised call centre, where a wide range of pharmacist interventions across a range of clinical conditions was already being delivered by telephone. As MM was delivered by a small team of pharmacists, we were able to train and supervise the clinicians more effectively than in a dispersed model in community pharmacies across all the participating sites in four regions in England, as had been envisaged in our initial plan. In addition, this centralised model allowed routine recording of all telephone-delivered MM sessions, and we monitored and rated a random sample of calls, stratified by pharmacist, in order to assess fidelity to the intervention and feedback into supervision where necessary. This meant that not only did the pharmacists develop a high level of skill in delivering the intervention, but we were also able to achieve a high level of fidelity to the planned intervention although it was being delivered to a large number of participants across a wide geographical area.

The CM intervention was also adapted from previous protocols that had been designed for use in treatment of substance use disorder, as well as published evidence from clinical trials in the alcohol field.<sup>70,71,89,92,153</sup> In the case of both the MM and CM interventions, we conducted extensive patient and clinician involvement in developing the manuals to ensure that both were acceptable and feasible to implement.

We were also able to develop an excellent working partnership with the manufacturers of acamprosate, Merck Serono, who supplied the medications for participants in this trial, dispensed through the network of Lloyds Pharmacies across the participating sites.

We developed a large network of participating community addiction treatment services across four regions in England (London, Yorkshire and Humber, West Midlands and South East), where all recruitment of trial participants took place. During the trial, addiction services nationally were under extreme pressure with reducing funding from local authorities and a considerable turnover in changes of contracts and providers.<sup>15</sup> This proved extremely challenging for participation in clinical research and resulted in delays in achieving full recruitment to the trial, and resulted in an extension to the trial of a year which was funded by NIHR.

Acamprosate prescriptions were commenced by community addiction teams, but there were also challenges in persuading general practitioners to continue to prescribe acamprosate for participants as intended in the protocol. This was in spite of the fact that acamprosate has been recommended as a first-line treatment for alcohol dependence for over 10 years.<sup>21</sup> We found that attitudes towards prescribing acamprosate were not as positive as we had expected, and NHS authorities in some local areas did not support acamprosate prescribing. In these instances, the community addiction services had to continue prescribing for participants, but this may have provided a disincentive to both clinicians and participants to continue prescribing up to and beyond the recommended 6-month period.

## Key findings

### *Recruitment and randomisation*

This study aimed to compare the effects of pharmacist-delivered MM, with and without incentivisation provided by CM, compared to SS. The primary hypothesis was that MM plus CM plus SS (SS + MM + CM), and MM plus SS without CM (SS + MM), would result in greater medication adherence than SS alone. We also hypothesised that SS + MM + CM would result in greater adherence to MM, as well as greater adherence to medication than SS + MM.

We were able to recruit 739 participants, of whom 372 (50%) were randomly allocated to the SS group, 182 (25%) to SS + MM group and 185 (25%) to SS + MM + CM group, achieving our planned recruitment target, although due to changes in service provider contracts, this took longer to achieve than planned. We also managed to successfully follow up 518 (70%) participants at the primary end point, achieving the planned statistical power. Our follow-up rate at 12 months was lower than planned but this had no influence on the primary outcome analysis.

Comparing the characteristics of participants across study arms at baseline showed no differences between allocated groups, suggesting that the randomisation method minimised bias.

### *Primary outcome analysis and sensitivity analyses*

As discussed in [Chapter 3](#), we were unable to use the primary outcome measure as intended due to various limitations of the MEMS and pill count data. We therefore used self-reported adherence as our primary outcome measure. The potential limitations of this are discussed below.

Our primary ATA showed that the mean difference in per cent adherence to acamprosate was 10.6% lower in the SS group compared to the SS + MM + CM group which was statistically significant. This was also close to the pre-specified clinically important difference. Although the mean adherence was 3.1% lower in the SS group compared to the SS + MM group, this was not statistically significant, and a similar non-significant finding was seen comparing SS + MM and SS + MM + CM groups, with SS + MM 7.9% lower than SS + MM + CM.

We found that 45 (6.1%) participants had been followed up outside of the 2-month follow-up window at the primary end point. A sensitivity analysis, however, showed that this had no impact on the primary outcome analysis. Similarly, both multiple imputation and a sensitivity analysis to explore the impact of missing data indicated that we can be confident that the observed treatment effects are robust under different interpretations of the nature of missing data.

A CACE analysis was conducted under two scenarios: scenario 1 where participants adhered to at least 6 (50%) of the MM calls, and scenario 2 where they adhered to 12 (100%). In scenario 1, 58% in the SS + MM group adhered to 50% of the MM calls, compared to 69% in the SS + MM + CM group. In scenario 2, 11% in the SS + MM group adhered to 100% of MM calls compared to 39% in the SS + MM + CM group. The CACE analysis showed that compared to our intention-to-treat analysis, under scenario 1, the difference between SS + MM + CM and SS increased from 10.6% to 12.4% greater adherence to acamprosate at month 6. Comparing SS + MM to SS, the previously non-significant difference (3.1%) became statistically significant within the CACE analysis at a difference of 13.2%.

Under scenario 2, the differences became larger in magnitude at 22.2% comparing SS + MM + CM with SS, and 31.8% comparing SS + MM with SS (although this latter analysis needs to be interpreted cautiously given the small number of participants in the analysis). So, in both scenarios 1 and 2, the benefits of SS + MM + CM were significant and clinically important. This was the case for SS + MM only when compliance was incorporated into the analysis.

### Secondary outcome analyses

The ATA analysis showed lower per cent days abstinent in SS compared to both SS + MM + CM and SS + MM, but these were not significant. However, when assessed under the scenario 2 CACE analysis, per cent days abstinent were significantly lower in the SS group compared with both SS + MM + CM and SS + MM groups. ATA analysis of other secondary outcome measures at both 6 and 12 months showed no significant differences between groups.

The analysis of compliance with MM calls showed that those who complied were significantly more likely to have improved alcohol use outcomes: 12.5% more per cent days abstinent in the SS + MM + CM group and 15.1% more in the SS + MM group compared to SS alone (although the differences in the SS + MM group should be taken with caution considering the small numbers involved). There was also a significant correlation between increased adherence to acamprosate and better drinking outcomes ( $r = 0.39$ ;  $p < 0.001$ ).

### Health economic analysis

The primary economic analysis was a cost-utility analysis where outcomes were expressed as QALYs, as recommended by NICE.<sup>129</sup> A secondary analysis explored cost-effectiveness in terms of the primary clinical outcome, which was adherence to relapse prevention medication. The primary economic perspective was the NHS/PSS perspective preferred by NICE. This covers all hospital, community health and social services. A sensitivity analysis based on a broader societal perspective, including impact on the criminal justice sector was planned. However, this became redundant because criminal activity was not reported by any patient at any time point.

Full service use data at the primary follow-up point of 6 months were available for 70% of the sample randomised, and 53% at the 12-month follow-up point. We found that SS + MM + CM participants attended more MM calls than the SS + MM group (mean of 7.7 vs. 6.1), and participants in the SS + MM + CM group received an average of 9 vouchers out of a possible 12, with 98% receiving at least one voucher. The SS + MM + CM group were prescribed acamprosate for a longer period compared to the SS + MM and SS groups at month 6, although this reduced and was broadly similar between groups by month 12.

The main difference in health and social care costs at month 6 was the SS + MM + CM group reported much less use of supported accommodation (primarily residential rehabilitation) than either the SS + MM or SS groups. The use of all other health and social care services was broadly similar across groups at month 6. At month 12, the SS + MM group reported greater use of supported accommodation than SS + MM + CM and SS, but the use of all health and social care services was similar across groups.

Differences in quality of life between groups and across time points were small, but favoured the SS + MM + CM and SS + MM groups over the SS group. This translated into small differences in QALYs which were significantly higher only for the SS + MM group over SS at 12 months.

The primary economic analysis found that SS + MM + CM was cost-effective compared to SS alone, but that SS + MM was not cost-effective compared to SS alone. SS + MM + CM dominated SS alone, achieving more QALYs at lower cost, with an 89% probability that SS + MM + CM was more cost-effective compared to SS over the NICE £20,000–30,000 cost per QALY threshold range. The cost per QALY benefit of SS + MM versus SS was at an additional cost of £151,250 per QALY which is well over the NICE threshold. The results were robust in the planned sensitivity analyses.

Secondary analysis based on the main clinical outcome of medication adherence showed that SS + MM + CM dominated SS, and SS + MM also achieved better medication adherence but at an additional cost of £329 per one additional per cent of medication adherence. At 12 months, both SS + MM + CM and SS + MM had a higher probability of being cost-effective than SS alone at the NICE cost-per-QALY thresholds of £20,000–30,000 while SS + MM had a higher probability of being cost-effective than SS alone at the £30,000 cost-per-QALY threshold. An analysis of cost-effectiveness modelled over 20 years amplified these findings and showed that the probability both SS + MM + CM and SS + MM were cost-effective compared to SS was 100% across all values of the NICE willingness-to-pay threshold of £20,000–30,000 per QALY.

## Consideration of possible explanations

While we found a clinically significant effect of SS + MM + CM compared to SS in terms of our primary outcome measure, medication adherence, we did not find a significant effect on alcohol consumption outcomes in the ATA, although this was the case in the CACE analysis. Arguably, from a clinical perspective, the benefit of increased medication adherence is only relevant if it translates into improved drinking outcomes. This is where our secondary analyses become important in understanding the potential mechanisms involved.

The CACE analyses showed that those participants who engaged with the MM calls not only had greater medication adherence but also had better drinking outcomes. These favoured both SS + MM and SS + MM + CM groups. So, our hypothesis is that MM has a positive impact on drinking outcomes in people who engage with it, through improved medication adherence.<sup>144</sup> CM has a positive impact on adherence with MM calls and, by doing so, an impact on both medication adherence and reduced drinking. This supports the hypotheses of the trial.

Furthermore, these clinical benefits translated into economic benefits. The analysis of service use data showed that SS + MM + CM group both attended more MM sessions, and took acamprosate for longer than the SS group. Also, the SS + MM + CM group used less residential rehabilitation than either the SS + MM or SS groups. This was also reflected in improvements in quality of life in the SS + MM + CM group compared to the SS group, and modelling the data over a 20-year time horizon, SS + MM + CM and SS + MM were both found to be cost-effective compared to SS alone.

Taking these findings together, this suggests that SS + MM + CM is the better intervention as a result of supporting better adherence with MM, which translates into improved acamprosate adherence,

improved drinking outcomes, and probably as a consequence, improved quality of life and reduced need for high-cost residential care. It is possible that MM as an intervention may have had benefits, in terms of reduced drinking and other outcomes, not exclusively because of its impact on medication adherence. Although medication adherence was the primary target of MM sessions, it was also designed to include other aspects of clinical support from the pharmacists, including encouragement to remain abstinent from alcohol and/or seek and engage with help from primary care and specialist addiction services where needed. So, the benefits of MM may be broader than simply improving medication adherence.

## Comparison with previous research

Our findings are broadly consistent with previous research on CM in both drug and alcohol dependence.<sup>143</sup> CM is strongly grounded in behavioural science and is one of the most widely studied intervention techniques in substance use disorder research.<sup>82,154</sup> CM is recommended by several international clinical guidelines as a key evidence-based intervention in substance use disorder, particularly for stimulant users.<sup>80,155,156</sup> Published systematic reviews have shown consistently larger effects of CM on treatment adherence than on abstinence outcomes in both drug and alcohol dependence, with effect sizes that are consistently greater for adherence than for abstinence.<sup>156</sup> One recent systematic review found the effect size across 10 CM studies to be 'moderate' ( $d = 0.47$ ; CI: 0.25 to 0.69) for adherence directed, and 'small' ( $d = 0.22$ ; CI: 0.12 to 0.33) for abstinence directed, CM.<sup>156</sup> This is consistent with our results, although our secondary analyses suggested that although the CM was, in our case, targeted at increasing attendance at MM sessions, it also had an effect on drinking outcomes. An intriguing possibility, and a suggestion of a recent review, is that it would be useful to consider combining CM directed at attendance with CM directed at abstinence, and to compare the effects of combined CM with individually directed CM and care as usual.<sup>156</sup>

Another target for CM in previous studies has been directly incentivising medication adherence rather than adherence to interventions directed at improving medication adherence, as in the ADAM trial. For example, there is evidence of CM directed at improving adherence to both methadone maintenance treatment and hepatitis B vaccination in opiate-dependent patients having a significant and cost-effective impact on outcomes.<sup>153,155</sup> We considered this application in the ADAM trial, but the challenge was to find a reliable method of measuring adherence to acamprosate. In the case of methadone and hepatitis B vaccination adherence, there are simple routine methods of measuring adherence which made this possible in these trials. Also, in those with substance use disorder, the availability and relatively low cost of urine and saliva drug testing lend itself to routine use in CM incentivising abstinence.

Some early clinical trials of acamprosate used urine analysis to detect acamprosate adherence, but this was considered too costly and impractical for routine clinical use, and hence, in this pragmatic clinical trial.<sup>26</sup> We also considered using the MEMS data as a way of measuring adherence to acamprosate. However, we considered this would also have some limitations, particularly in routine clinical care, and indeed the lack of reliable data from MEMS over an extended period of monitoring in this trial vindicated that decision.

The reliable measurement of abstinence is also challenging in alcohol-dependent patients due to the short half-life of ethanol, and the low reliability of existing blood markers of alcohol consumption.<sup>157</sup> Therefore, using CM to directly incentivise abstinence from alcohol is not yet technically possible. But the development of wearable transdermal alcohol sensors may allow the development of this approach in the future.<sup>89</sup> Taken together, because of these limitations, we decided to use CM to incentivise adherence to MM sessions which could be reliably measured, rather than having medication adherence itself or alcohol abstinence as the CM target.

Previous reviews have pointed to evidence that the effects of CM often decay once they are discontinued and indeed we found that in this trial.<sup>158</sup> CM was only applied up to the 6-month point, where its beneficial effects were found. Thereafter there was some regression to the mean across groups. This is by no means unique to CM; trials of other psychological and pharmacological interventions in the drug and alcohol dependence field report a similar decay over time. Stitzer<sup>159</sup> and others<sup>72</sup> have raised the possibility of longer-term CM interventions, including the possibility of an 'incentives maintenance model, outreach efforts designed to monitor, detect and retreat relapsed clinicals or a combination of CM with cognitive-behavioural therapies'.<sup>159</sup>

Previous research has shown that psychosocial interventions to increase medication adherence are effective across a range of clinical conditions and medications.<sup>158,160</sup> While the 'medical management' approach, adapted for this trial in the form of MM, has been used in several trials of pharmacotherapy for alcohol dependence, its effectiveness and cost-effectiveness were unknown.<sup>146-151</sup> Our results show that MM enhanced with CM was more effective than SS in increasing relapse prevention medication adherence and had a higher probability of being cost-effective (at 6- and 12-month follow-up and when modelled over 20 years). However, MM alone was not more effective than SS. We did find evidence that patients who engaged with MM had better adherence than those who did not, and the cost-effectiveness analyses favoured MM compared to SS at 12-month follow-up and when modelled over 20 years.

## Strengths and limitations

The strengths of this study include that it was a pragmatic, multicentre RCT conducted in a diverse population across four regions in England and had adequate statistical power to detect treatment effects. There was a relatively low level of exclusions compared to other alcohol trials, and withdrawals were few. We were able to train a relatively small and stable team of pharmacists to deliver the MM intervention across a wide geographical area cost-effectively, and we were able to maintain a high level of fidelity to the intervention manual through monitoring of intervention calls and regular supervision.

The baseline data show that our randomisation process created equal groups and we used validated outcome measures to assess outcomes. We were able to achieve our target follow-up rate at the primary outcome end point. Further, the trial included an evaluation of cost-effectiveness, which has been the case in few previous studies of relapse prevention medications, and the bespoke economic model was able to assess impacts across a 20-year time horizon, far longer than is common in other alcohol clinical trials which typically are restricted to a 1-year time frame.<sup>21</sup> Given that for many people, alcohol dependence is a chronic relapsing condition, this longer time frame is arguably more meaningful than shorter time frames in terms of likely real-world impact.

The trial also had a number of weaknesses. We intended to use a hierarchy of medication adherence measures to assess the primary outcome, with MEMS as a 'medium', and pill count and self-report as 'low', confidence measures of adherence. In implementation, we found that it was not possible to obtain reliable MEMS measures for the majority of participants. This was likely due to a number of factors, principally the large number of pills that needed to be taken each day, making the process unwieldy for participants, resulting in poor compliance with the recommended process – for example, we became aware that some participants were taking a day's or a week's supply from the MEMS bottles at a time rather than twice or three times per day, or stopped using MEMS altogether, meaning that the MEMS data most likely underestimated the true level of adherence.

Similarly, we had problems in implementing the pill count measure because of the large number of retail pharmacies involved in dispensing the medication across multiple sites, and consequent difficulties in ensuring pharmacist adherence to the protocol in relation to pill count. We also had difficulties with

participants failing to bring used medication packs to collect new prescriptions, or receiving medications by mail rather than in-person.

Therefore, both MEMS and pill count were not considered a reliable source of data on adherence, and we relied on the self-report measure as our primary outcome measure as being the most reliable and consistent measure available across participants. However, it is worth noting that although self-report is a 'low' confidence measure in terms of medication adherence, it is the preferred method of measuring the other main primary outcome in most alcohol clinical trials, namely self-reported alcohol consumption, where it has been shown to have a high level of reliability compared to other outcome measures.<sup>161</sup> Also, there is evidence that self-report is a valid and reliable method for estimating adherence, and that self-report estimates of shorter periods are reliable proxies for adherence over longer periods for people with chronic conditions.<sup>127,128</sup>

Another limitation was the follow-up of a small proportion (6.1%) of participants beyond the 60-day follow-up time frame at 6 and 12 months. This had the potential to introduce bias into the analysis of outcome, in that participants followed up later than planned may have differed from those followed up within the time window. However, a sensitivity analysis showed that this had no impact on the outcome result, and so all participants were included in the primary analysis. We also had a lower than planned follow-up rate at the 12-month outcome end point, which may have reduced the statistical power to detect differences in the secondary analyses, while having no impact on the primary outcome findings.

## Patient and public involvement

Please see [Chapter 2](#) for a description of the involvement of patients and the public in the development of the trial interventions. There has not been service user involvement in the interpretation of the main trial results. We worked with a service user representative to write the plain language summary of this report.

## Conclusions

### Generalisability

The study had minimal exclusion criteria compared to some other trials of relapse prevention medications and a large proportion of those approached to participate were both eligible and gave consent to take part. Given the large and diverse range of community addiction services in four regions across England from which participants were recruited, including both NHS and third sector treatment providers in urban, metropolitan and suburban/semi-rural areas, we are confident that our participants were representative of patients attending typical services in England at the time of the study. Participants had to be recently detoxified from alcohol in order to be eligible, so the sample will not be representative of all patients attending addiction services. However, they will be generally representative of people for whom initiation of acamprosate prescribing is recommended by NICE.

### Implications for health care

#### Importance of adherence

Alcohol relapse prevention medications such as acamprosate have a strong evidence base and are recommended for routine use in clinical practice in the UK and many other countries.<sup>21,162-165</sup> However, it is also known that adherence to these medications is suboptimal, which limits their potential to reduce relapse and improve treatment outcomes. Yet, until now, little attention has been paid to finding effective and cost-effective methods to enhance medication adherence in alcohol dependence. We and others have shown that better outcomes are achieved with greater medication adherence. We have also shown a relationship between adherence to MM and

medication adherence, and MM is more effective when it is reinforced by CM. Both MM and MM combined with CM are cost-effective compared to standard care within NICE parameters at 12-month follow-up and when modelled across a 20-year time horizon. Our findings suggest that addiction services should incorporate CM and MM methods to enhance medication adherence into routine clinical practice to improve patient outcomes.

### **Partnerships with pharmacy**

There has been an increasing focus on the extension of the role of pharmacists beyond medication supply to improve public health, and this has been endorsed in the UK by several Government reports and initiatives, including the HLP and Public Health England. We managed to develop an effective working partnership with Lloyds Pharmacy, capitalising on existing expertise and infrastructure to implement the pharmacist-delivered MM intervention. That we were able to do so efficiently through an existing pharmacy call centre team across a wide geographical area, cost-effectively, points to the potential to expand this provision beyond this multicentre trial. This will require the development of greater partnerships between pharmacy, NHS and third sector addiction treatment providers. Advances have already been made in integrating pharmacy-delivered interventions for substance use disorder and smoking cessation, although these have recently been inhibited by changes in commissioning arrangements and cuts to the national public health budget. Nevertheless, this trial should encourage greater partnership working, training and new initiatives to extend the role of pharmacists in addiction treatment.

### **Partnerships with primary care**

Although relapse prevention medications, including acamprosate, have been recommended by NICE for over a decade, uptake and coverage have been slow, such that only a small proportion of patients who could benefit from pharmacotherapy actually receive these effective medications. Part of this may be a lack of awareness among clinicians in both primary and secondary care of the benefits to patients of acamprosate and naltrexone, at relatively low cost. We also became aware during this trial that some general practitioners are unwilling to prescribe acamprosate even if it has been initiated and recommended by a specialist addiction service, and in some areas, acamprosate was not approved by local NHS commissioners even although it is cost-effective and approved by NICE. For some participants, the specialist addiction service had to continue prescribing medication beyond the usual treatment period due to the reluctance of general practitioners to take on prescribing. This may have limited the length of prescribing for some participants, and at a minimum, a lack of endorsement by patients' GPs may have affected patient attitudes to the value of continuing for the duration recommended by NICE. We feel there is a need for greater education and awareness of the benefits of relapse prevention medications, such as acamprosate, and it should be routinely available and funded by the NHS and local authority commissioning across the UK.

### **Implications for research**

#### **The importance and feasibility of alcohol clinical trials**

Relatively few trials of clinical interventions in alcohol dependence have been funded or conducted in the UK, with the consequence that many of the current treatment guidelines rely on evidence from other countries, mostly the USA, where the health systems may differ in important ways. This may be partly because alcohol use disorders are not seen as a sufficiently important public health area to research. However, there is ample evidence that while morbidity and mortality from most non-communicable diseases are decreasing in the UK, alcohol-attributable diseases are increasing, as are alcohol-related hospital admission rates.<sup>166</sup> One-fifth of all hospital admissions in England are alcohol related.<sup>167</sup> Therefore, greater research, and in particular clinical trials, are needed to find effective and cost-effective ways of reducing this increasing burden on society.

Another reason for the lack of alcohol clinical trials in the UK may be due to a perception that it is not possible to conduct clinical trials in alcohol-dependent populations. It is certainly true that we encountered many challenges in conducting this trial. However, these were mostly due to structural problems in the commissioning of clinical services, with frequent tendering of services and changes of provider through the course of the trial. This had an impact on our ability to recruit to the trial. There were also challenges in accessing relevant NHS research funding streams, such as research support costs to conduct research in third sector organisations. Even in relation to NHS providers, we were unable to obtain any excess treatment costs for this trial, in spite of repeated efforts, which delayed recruitment and provided a disincentive for providers to participate. Given the changing landscape of health-care provision in England including greater private and third sector provision, not only in the addiction field, but consideration should also be given to facilitating clinical research across the health system beyond simply the NHS.

Nevertheless, we have been able to demonstrate that it is possible to deliver a large multicentre, multisector clinical trial in alcohol dependence with adequate statistical power, and of relevance to clinical practice. There is a need to commission more clinical trials in alcohol dependence to develop the evidence base necessary to guide clinical and policy decision-making in the UK health system.

### **Potential of CM in alcohol dependence**

Since we started developing this trial, the evidence base on CM in addictions has continued to grow both in the UK and internationally.<sup>148,164</sup> However, there remain relatively few trials of CM in alcohol dependence compared with substance use disorder, which is surprising given the large and growing findings in relation to its effectiveness in substance use disorder. We were also able to implement CM relatively easily in routine clinical practice. It does not require a high level of skill to deliver and it can be done cost-effectively and at relatively low cost compared to most of the recommended psychosocial interventions for alcohol dependence. This current trial should prompt greater investigation of the potential of CM in alcohol dependence, including its use in reinforcing both adherence to psychosocial interventions and in promoting abstinence or reduced alcohol consumption. There is evidence for its effectiveness for both applications in the substance use disorder field. Given our findings in relation to CM enhancing MM adherence, future trials should be developed to explore its effectiveness with other alcohol interventions where there is evidence of poor adherence.



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**Eileen Brobbin** (<https://orcid.org/0000-0001-8464-4847>) (Research Assistant and PhD Student) responsible for recruitment and data collection for the London site. Involved in the writing and review of the final report.

**Sarah Byford** (<https://orcid.org/0000-0001-7084-1495>) (Professor, Health Economics) was a co-applicant involved in the conception and design of the trial, was responsible for the health economic component of the trial and line management of the health economist, contributed to the drafting of the economic sections of the final report and commented on the full report.

**Rachel Coleman** (<https://orcid.org/0000-0003-3404-0839>) (PhD Student) involved in Yorkshire and Humber site set up, participant recruitment and data collection. Reviewed and commented on the final report.

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**Maria-Leoni Koutsou** (<https://orcid.org/0000-0002-4599-9853>) (Project Manager) responsible for recruitment, data collection at baseline and follow-up time points.

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## Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

## Ethics statement

Ethical approval has been granted by the East of England – Cambridge South Research Ethics Committee (Ref: 15/EE/0308). All participants will give written informed consent to take part in the research.

## Permissions

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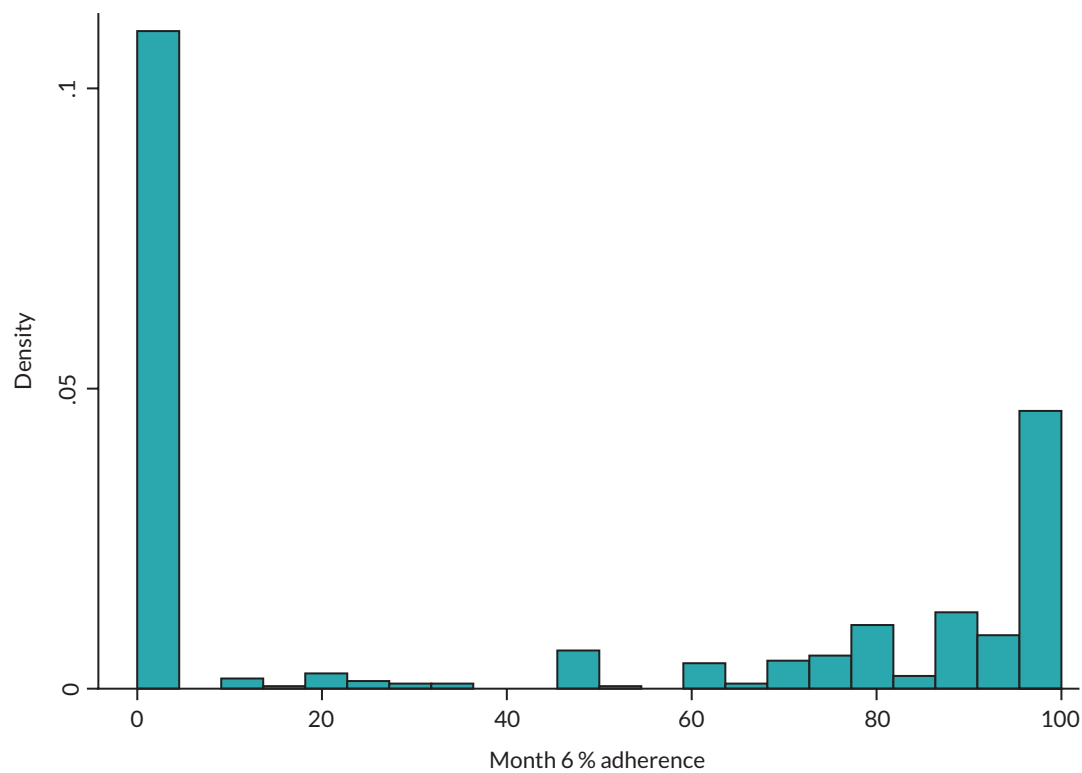
## Appendix 1 Additional statistical output

**TABLE 23** Outcomes by allocated group at 2 and 4 months

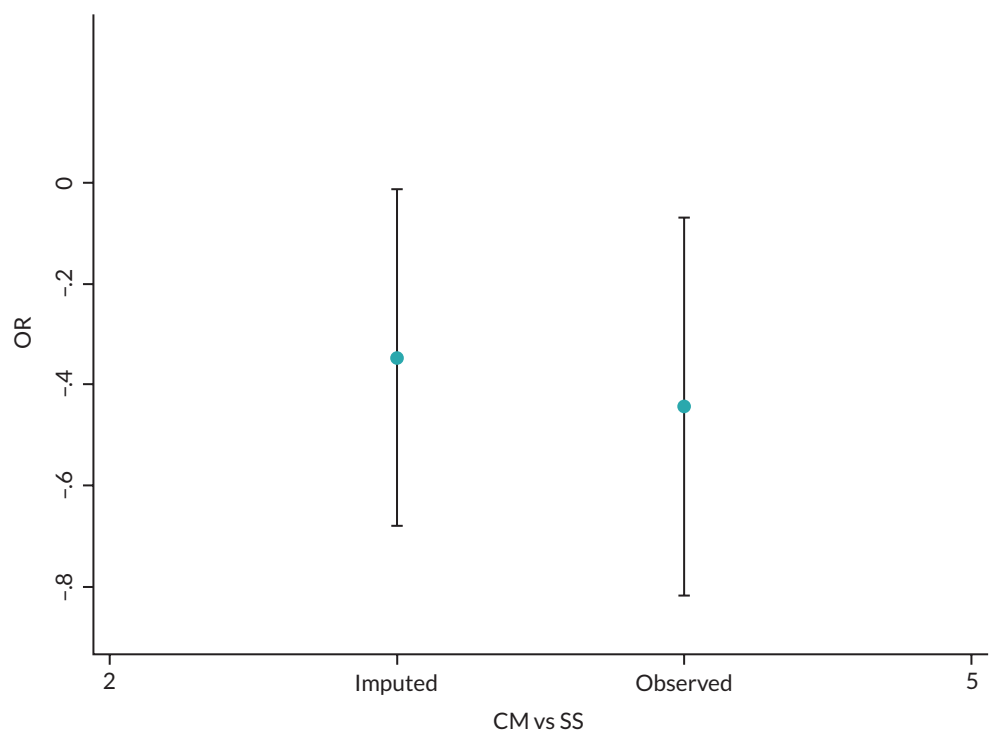
	Month 2			Month 4		
	SS + MM + CM (n = 123)	SS + MM (n = 109)	SS alone (n = 231)	SS + MM + CM (n = 118)	SS + MM (n = 102)	SS alone (n = 221)
Prescribed acamprosate, n (%)	113 (91.8)	93 (85.3)	230 (99.6)	88 (74.6)	67 (65.7)	138 (62.4)
Mean % adherence (SE)	84.6 (2.4)	80.7 (2.9)	74.6 (2.3)	82.7 (2.7)	74.6 (4.1)	72.7 (2.6)
Mean MMAS-8 (SE)	5.6 (0.14)	5.3 (0.16)	5.2 (0.11)	5.7 (0.15)	5.3 (0.18)	5.1 (0.13)

**TABLE 24** Baseline and month 6 outcomes for those followed up within frame, and those not

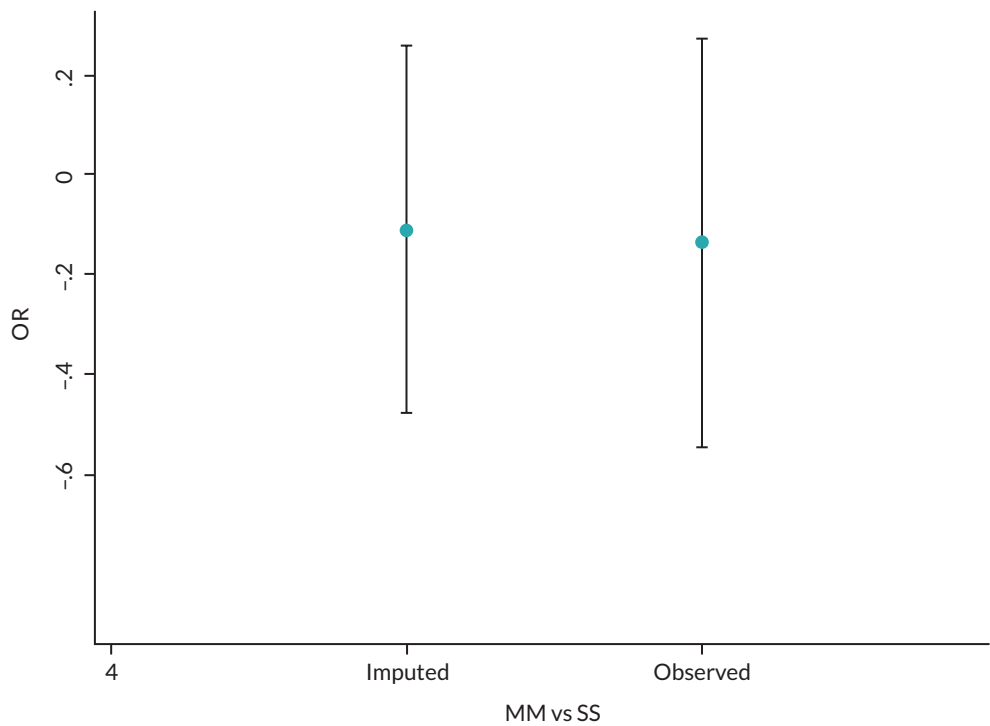
	Within tolerance n = 695 (93.9%)	Without tolerance n = 45 (6.1%)
Site, n (%)		
Birmingham	206 (92.4)	17 (7.6)
Central and North West London	153 (98.1)	3 (1.9)
South East London	69 (94.5)	4 (5.5)
Southampton	88 (93.6)	6 (6.4)
Yorks	179 (92.3)	15 (7.7)
SADQ, n (%)		
≤ 30	279 (93.9)	18 (6.1)
30 plus	416 (93.9)	27 (6.1)
Allocation, n (%)		
SS	347 (93.3)	25 (6.7)
SS + MM	173 (95.0)	9 (5.0)
SS + MM + CM	175 (94.1)	11 (5.9)
Per cent adherent at month 6		
Mean (SD)	0.44 (0.45)	0.21 (0.38)
Median (IQR)	0.25 (0; 0.95)	0 (0; 0)
PDA at month 6		
Mean (SD)	0.72 (0.38)	0.65 (0.40)
Median (IQR)	0.97 (0.43; 1.00)	0.93 (0.24; 1.00)



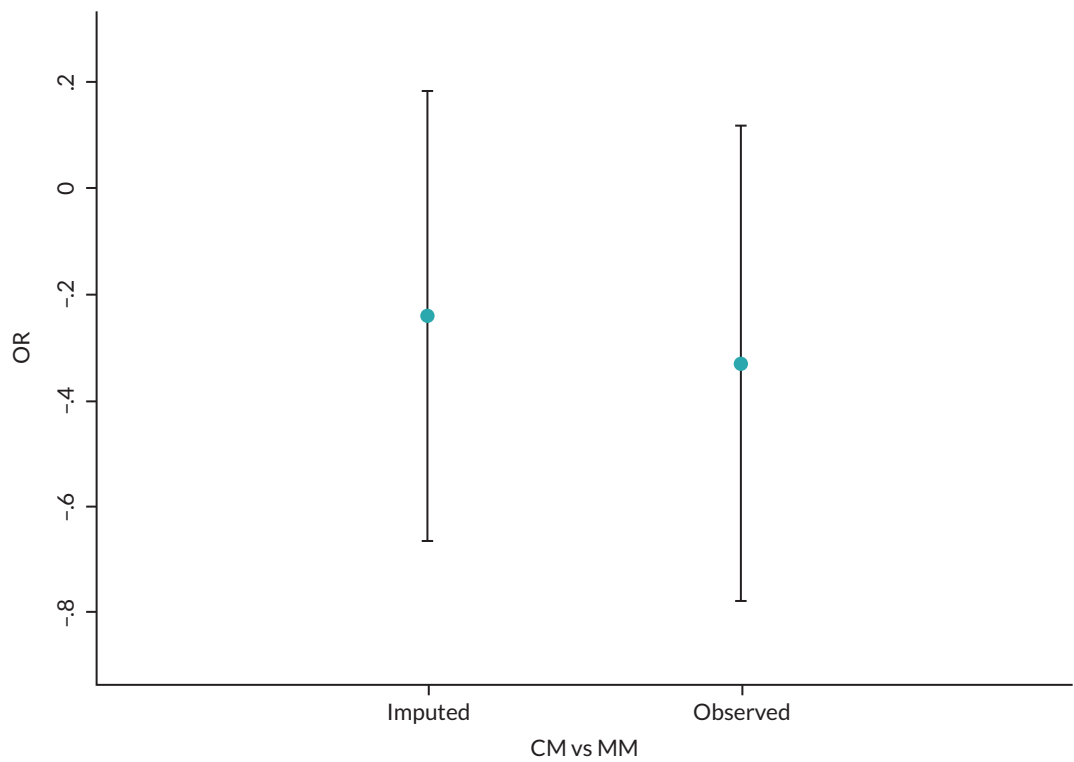
**FIGURE 20** Distribution of primary outcome, per cent adherence to acamprosate at month 6.



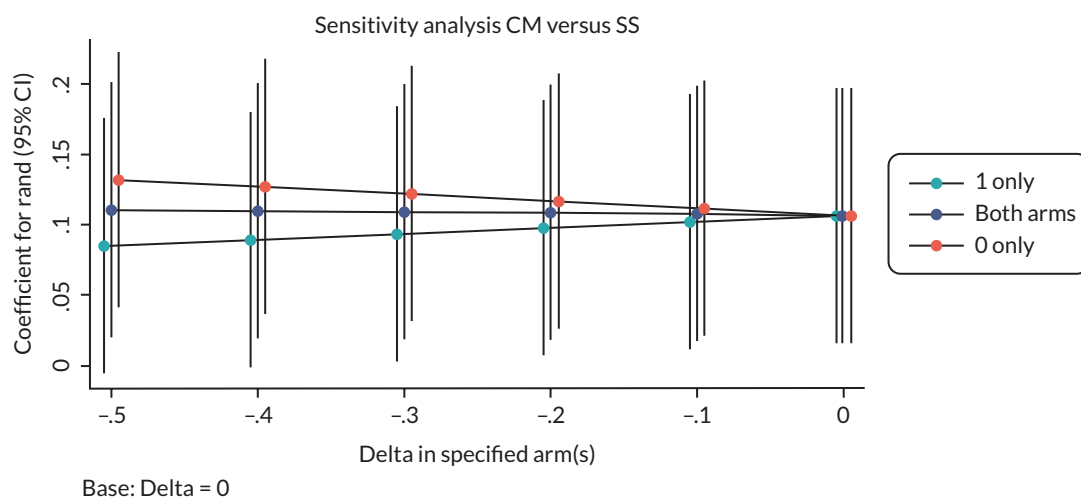
**FIGURE 21** SS + MM + CM vs. SS comparison of observed and imputed odds ratio and 95% CI for per cent days adherence at month 6.



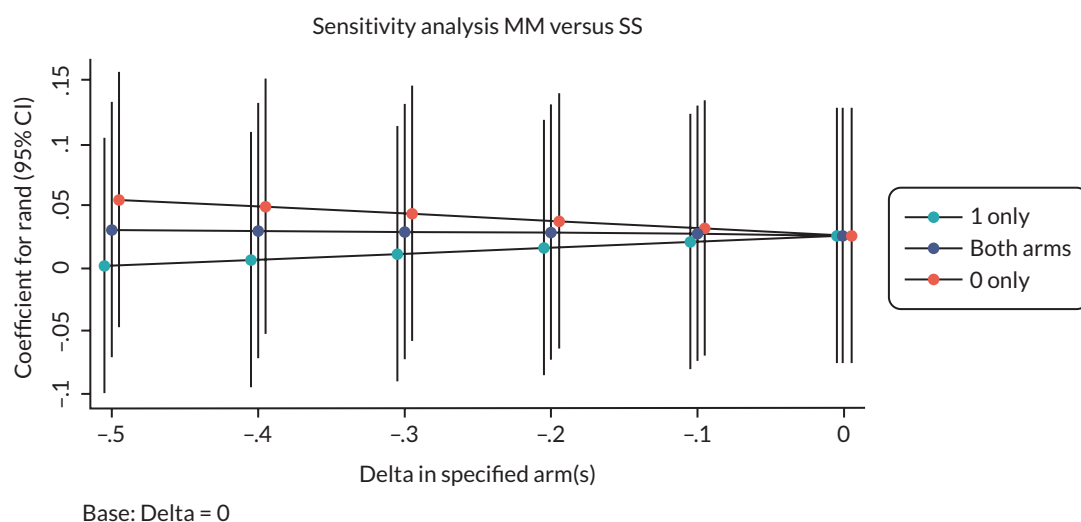
**FIGURE 22** SS + MM vs. SS comparison of observed and imputed odds ratio and 95% CI for per cent days adherence at month 6.



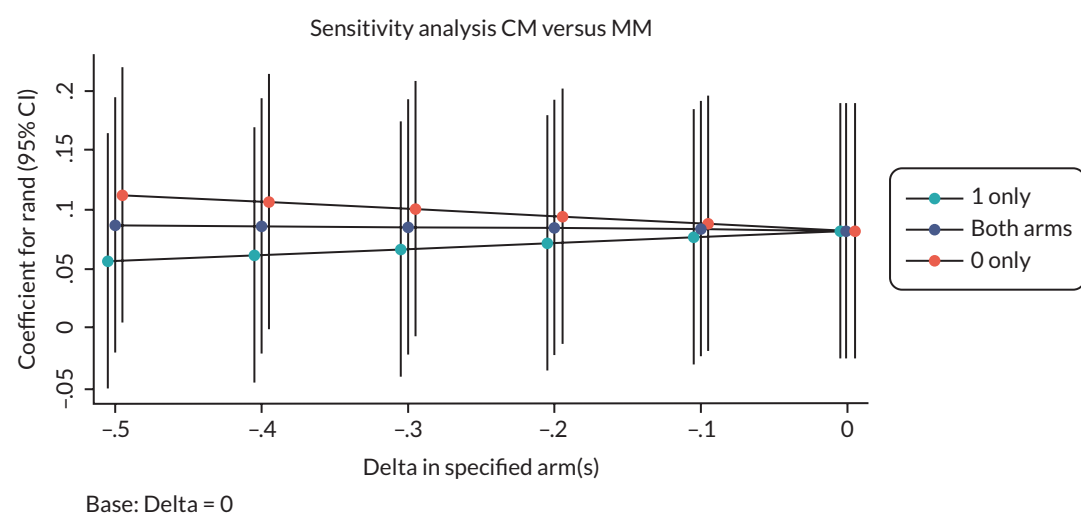
**FIGURE 23** SS + MM + CM vs. SS + MM comparison of observed and imputed odds ratio and 95% CI for per cent days adherence at month 6.



**FIGURE 24** SS + MM + CM vs. SS sensitivity analysis of missing data modelled by varying delta between -0.5 and 0.



**FIGURE 25** SS + MM vs. SS sensitivity analysis of missing data modelled by varying delta between -0.5 and 0.



**FIGURE 26** SS + MM + CM vs. SS + MM sensitivity analysis of missing data modelled by varying delta between -0.5 and 0.

Analysis indicating odds ratio, marginal effects (95% CI) of predictors of % adherence at month 6 derived from a fractional regression. Variables excluded if no evidence of association.

Fractional logistic regression

Number of obs = 517

Wald chii2 (13) = 40.00

Log pseudolikelihood = -333.538

Prob > Chi2 = 0.0001

**TABLE 25** Prognostic analysis of predictors of medication adherence at month 6

M6_frac_pcad	Odds ratio	Robust Std. Err.	Z	p >  z	95% CI	
StudyArm						
SSMM	0.723	0.168	-1.39	0.164	0.458	1.140
SS	0.600	0.115	-2.66	0.008	0.412	0.875
Site						
Central and North West London	0.848	0.199	-0.70	0.483	0.535	1.344
South East London	0.438	0.151	-2.40	0.017	0.223	0.861
Southampton	0.919	0.251	-0.31	0.757	0.538	1.570
Yorkshire and Humber	0.950	0.214	-0.23	0.820	0.611	1.477
Children						
Yes-resident	0.759	0.178	-1.18	0.239	0.479	1.202
Yes-non-resident	1.250	0.265	1.05	0.292	0.825	1.894
Age	1.014	0.009	1.48	0.140	0.996	1.032
Age_first_drink	1.034	0.019	1.80	0.072	0.997	1.072
n0apqaffect	0.851	0.070	-1.95	0.052	0.724	1.001
n0apqcommo	1.016	0.032	0.52	0.604	0.956	1.081
n0auq	0.816	0.071	-2.34	0.019	0.688	0.967
_cons	0.674	0.429	-0.62	0.536	0.194	2.346

SS, Standard Support; SSMM, Standard Support + Medication Management

**Note**

cons estimates baseline odds.

Analysis indicating odds ratio, marginal effects (95% CI) of predictors of PDA at month 6 derived from a fractional regression. Variables excluded if no evidence of association.

**TABLE 26** Prognostic analysis of predictors of PDA at month 6

M6_frac_pda	Odds ratio	Robust Std. Err.	z	p >  z	95% CI	
StudyArm						
SSMM	0.975	0.265	−0.09	0.927	0.572	1.662
SS	0.781	0.174	−1.11	0.269	0.504	1.210
Site						
Central and North West London	1.068	0.278	0.25	0.801	0.641	1.780
South East London	0.672	0.224	−1.19	0.232	0.50	1.290
Southampton	1.171	0.349	0.53	0.596	0.653	2.100
Yorkshire and Humber	1.468	0.421	1.34	0.181	0.837	2.574
n0auq	0.848	0.070	−1.99	0.047	0.721	0.998
n0PDA	1.008	0.006	1.27	0.203	0.996	1.020
n0PD15plus	0.992	0.005	−1.64	0.100	0.982	1.002
_cons	4.208	2.477	2.44	0.015	1.328	13.336

**Note**

\_cons estimates baseline odds. SSMM = Standard Support + Medication Management, SS = Standard Support



EME  
HSDR  
**HTA**  
PGfAR  
PHR

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