**Title:** Cost-effectiveness of low-dose amitriptyline for irritable bowel syndrome in primary care.

**Short title:** Cost-effectiveness of amitriptyline for IBS.

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**Abbreviations:**

| | |
|---|---|
| HRQoL | health-related quality of life |
| IPW | inverse probability weighting |
| IBS | irritable bowel syndrome |
| IBS-C | irritable bowel syndrome with constipation |
| IBS-D | irritable bowel syndrome with diarrhoea |
| IBS-M | irritable bowel syndrome with mixed bowel habits |
| IBS-U | irritable bowel syndrome unclassified |
| IBS-SSS | Irritable Bowel Syndrome Severity Scoring System |
| ICER | incremental cost-effectiveness ratio |
| NHS | National Health Service |
| NHB | net health benefit |
| NICE | National Institute of Health and Care Excellence |
| NIHR | National Institute for Health and Care Research |
| PHQ-12 | Patient Health Questionnaire-12 |
| QALY | quality-adjusted life year |
| RCT | randomised controlled trial |
| TCA | tricyclic antidepressant |
| VAS | visual analogue scale |
| WSAS | Work and Social Adjustment Scale |

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**Specific author contributions:** ACF conceived and designed the ATLANTIS trial and had overall responsibility in his role as co-chief investigator. AW-H provided statistical input into the implementation and statistical analysis plan, under the supervision of AJF. SLA contributed to the design of the trial, participant enrolment, and data acquisition. P-LO provided statistical input into the implementation and statistical analysis plan, under the supervision of AW-H and AJF. MJR and RF contributed to the design of the trial, participant enrolment, and data acquisition. FLB designed and implemented the nested qualitative study and supervised the qualitative analysis. MC provided PPI input in the design, implementation, and trial reporting. CF implemented the trial and contributed to the co-ordination of data acquisition and trial reporting. EAG contributed to the design of the trial. DH and GG contributed to the acquisition of health economic data and performed the analysis. DPM provided PPI advice to inform the design and trial reporting. AJF conceived and designed the ATLANTIS trial, was responsible for its overall implementation across Leeds Clinical Trials Research Unit and supervised the statistical analysis. HAE conceived and designed the ATLANTIS trial, contributed to participant enrolment, and data acquisition and had overall responsibility in her role as co-chief investigator. GG, ACF, HAE, and DH drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript. GG, DH, AW-H, and P-LO had full access to, and verified, all the data in the study. GG, ACF, HAE, and DH had final responsibility for the decision to submit for publication. DH is guarantor of the article.

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**Keywords:** irritable bowel syndrome

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**ABSTRACT**

**Background**: General practitioners rarely prescribe amitriptyline for irritable bowel syndrome (IBS) despite using it for other conditions, such as chronic pain. The ATLANTIS trial found low-dose titrated amitriptyline was a safe and clinically effective second-line treatment for IBS in primary care.

**Objective:** To undertake a pre-specified cost-effectiveness analysis of ATLANTIS trial data using National Institute of Health and Care Excellence reference case guidelines for England.

**Design:** A complete case and a full trial population analysis were undertaken using multiply imputed data with analyses at 6 (365 participants complete case, 463 participants full trial population) and 12 (224 participants complete case, 291 participants full trial population) months. As the trial was no longer fully randomised between 6 and 12 months, we adopted inverse probability weighting (IPW) to mitigate potential impact of participants choosing to continue trial medication.

**Results:** At a 6-month time horizon, complete case analysis demonstrated that low-dose amitriptyline was more likely to be cost-effective than not (incremental net health benefit (NHB) 0.0029 quality-adjusted life years (QALYs) per person, low-dose amitriptyline dominant, 67.3% probability cost-effective), but not in full trial population analysis. At 12 months, all analyses demonstrated low-dose amitriptyline was more likely to be cost-effective than not (complete case: incremental NHB 0.00757 QALYs per person, low-dose amitriptyline dominant, 81.7% probability cost-effective; full trial population analysis: incremental NHB 0.00388 QALYs per person, low-dose amitriptyline dominant, 68.7% probability cost-effective).

**Conclusions:** In addition to the clinical benefit, safety, and acceptability of low-dose amitriptyline in patients with IBS found in the ATLANTIS trial, these results indicate this inexpensive medication is likely to be cost-effective as a second-line treatment for IBS in

primary care over 12 months. This strengthens amitriptyline as a treatment option for people with ongoing IBS symptoms.

**Trial registration:** ISRCTN (ISRCTN48075063).

## INTRODUCTION

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction,[1] characterised by abdominal pain associated with a change in stool form or stool frequency.[2] The pathophysiology is not fully understood.[3] IBS affects 5% of the global population.[4, 5] Impairment in quality of life is comparable to that of patients with other chronic diseases, such as stroke or chronic obstructive pulmonary disease.[6] The annual direct costs of IBS in the UK are estimated at £1 billion.[7] Furthermore, indirect costs arise because people with IBS often have difficulties in working due to their condition.[8]

In the UK, treatment of IBS in primary care, as recommended by the National Institute of Health and Care Excellence (NICE) guideline,[9] consists of lifestyle adjustments, such as increasing levels of physical activity or making dietary changes, followed by the offer of first-line medications, including antispasmodics, antidiarrhoeals, or laxatives. This guideline states that low-dose antidepressant drugs, such as amitriptyline, a tricyclic antidepressant (TCA), which is used in secondary care for IBS because of its effects on motility and pain sensation, be considered if symptoms do not improve with first-line measures.

Although a previous meta-analysis of randomised controlled trials (RCTs) suggested a benefit of TCAs for IBS,[10] most trials were conducted in secondary or tertiary care.[11, 12] Surveys reveal general practitioners do not use these drugs often to treat IBS,[13] despite using them commonly for other conditions, such as insomnia.[14] ATLANTIS (Amitriptyline at Low-Dose and Titrated for Irritable Bowel Syndrome as Second-Line Treatment) was a double-blind placebo-controlled trial conducted in 463 patients with Rome IV-defined IBS across 55 general practices in England. Participants were randomised to 6 months of low-dose amitriptyline, commencing at 10mg once daily and self-titrating to a maximum of 30mg once daily, or placebo.[15] Low-dose amitriptyline was superior to placebo across multiple symptom-based outcomes for IBS, was more acceptable to patients than placebo, and was

well-tolerated, with most side effects being mild to moderate and occurring no more frequently than with placebo.[16-18] The majority of participants recruited consented to 12-month study participation, consisting of an initial 6 months of trial medication with the option to continue this for a further 6 months. Treatment duration and follow-up was curtailed to 6 months for later recruits, due to protocol changes required during the COVID-19 pandemic.

We report a within-trial economic analysis to investigate the cost-effectiveness of amitriptyline versus placebo as second-line treatment for IBS in primary care, up to a time horizon of 12 months, as pre-specified in the trial protocol.[15]

## METHODS

As ATLANTIS was based in England, the NICE reference case was used to determine the adopted methods and scope of the health economic analysis.[19] Direct costs and outcomes of patients randomised to each study arm, either low-dose amitriptyline or placebo, were compared over 6 months in a primary analysis and, for those opting to continue trial medication for a further 6 months, an analysis over the full 12 months of the trial. As the time horizon of the study was 12 months, no discounting of costs or benefits was required. We provide details on incremental costs from the perspective of health and personal social service providers, sourcing cost data from official publicly available records. In our baseline analysis, we applied a willingness-to-pay threshold of £20,000 per quality-adjusted life year (QALY) gained. Methods for dealing with missing data are provided in the online-only materials.

### Costing of resource use and cost sources

Usage of all resources and medications, including intervention costs, was collected through a resource utilisation questionnaire,[15] administered at baseline, 3 months (covering recall of the previous 3 months), 6 months (covering recall of the previous 3 months) and, for those consenting to continued participation, 12 months (covering recall of the previous 6 months). Reported healthcare utilisation was combined with unit cost information. Unit costs for resources were obtained from national sources: the Personal Social Services Research Unit Costs of Health and Social Care for primary and social care,[20] National Health Service (NHS) costs for secondary care,[21] and the NHS Drug Tariff for medications (see Supplementary Tables 1 and 2 for details).[22]

**Estimation of outcome measures**

Health outcomes were measured in QALYs, a generic metric of health that considers the length of life and the quality of life, such that one QALY is equal to 1 year of life lived in a state of full health.[23] Health-related quality of life (HRQoL) was estimated using EQ-5D-3L responses,[24] obtained at baseline, and at 3, 6, and 12 months. Total QALYs were derived by integrating HRQoL with durations, using a linear interpolation method to calculate the area under the curve. The primary outcome measure used for this analysis was incremental net health benefit (NHB), calculated as:

$$\text{Incremental NHB} = \left(\text{QALYs}_{\text{amitripyline}} - \text{QALYs}_{\text{placebo}}\right) - \left(\frac{\text{Costs}_{\text{amitripyline}} - \text{Costs}_{\text{placebo}}}{\text{Cost} - \text{effectiveness threshold}}\right)$$

In our primary analysis, a lower limit of the cost-effectiveness threshold of £20,000, recommended by NICE, was used to estimate NHB. Although health economic analyses often focus on an outcome measure of an incremental cost-effectiveness ratio (ICER), calculated from the difference in costs between treatment arms divided by the difference in QALYs between treatment arms, the use of this is primarily when the analysis is expected to obtain results where there are both positive incremental costs and positive incremental QALYs. When either or both of these is not the case, use of an ICER is complicated by interpretation issues.[25] Nevertheless, ICERs are provided with, where necessary, a note on their interpretation.

**Cost and utility models**

Estimates of differences in costs and effects between treatment arms were generated in a primary analysis using seemingly unrelated regression analysis. Even though an RCT design allows for balancing of baseline characteristics between treatment arms, some

differences may remain. Particular importance is attached to differences in the outcomes of interest (or components in the outcomes of interest): utility values and resource use at baseline, with such variables included as adjustment variables in regression-based estimates of differences in effects and costs between treatment arms.[26, 27] For this reason, both cost and QALY regression analyses were adjusted for the following stratification variables: recruitment hub (West Yorkshire, West of England, or Wessex), IBS subtype (IBS with constipation (IBS-C), diarrhoea (IBS-D), mixed bowel habits (IBS-M), or unclassified (IBS-U)) and baseline depression score on the Hospital Anxiety and Depression Scale,[28] as well as baseline costs (in cost regressions) and baseline HRQoL (in utility regressions).

**Dealing with missing data**

Missing data typically involved a lack of patient-reported primary care usage. We assumed that costs were missing for a given time point only where either the entire questionnaire had been returned blank or where the patient was lost to follow-up. In these instances, we imputed the entire costs associated with all types of resource use. Patients could, therefore, have missingness (and imputed costs) at one time point but not at others. In such cases, where available, costs were preferentially used and combined with imputed values at other time points. Similarly, HRQoL was imputed where absent for any given time point, combined with actual values where possible, and used to estimate QALYs.

In instances where complete data for all dependent and independent variables were not present, we employed multiple imputation by chained equations using predictive mean matching to address missing outcomes. This was used to generate estimates of missing values based on the distribution of observed data, as recommended in guidelines for cost-effectiveness analysis alongside clinical trials.[29] In accordance with the statistical analysis plan,[16] imputation models by treatment arm used the following variables: minimisation

factors (recruitment hub, IBS subtype, baseline HADS-depression score), age, sex, treatment status at 6 months, baseline IBS Severity Scoring System (IBS-SSS) score,[30] baseline Patient Health Questionnaire-12 (PHQ-12) score,[31] and baseline Work and Social Adjustment Scale (WSAS) score.[32] In addition to these, resource use at preceding timepoints was included in cost regressions, and HRQoL measures at preceding timepoints were included in QALY regressions.

**Cost-effectiveness analysis**

The cost-effectiveness analysis adopted an intention-to-treat perspective for summarizing and analysing health economic data. This consisted of a cost-utility analysis over the 6-month trial period, and the full 12-month follow-up. Following NICE guidance,[19] this evaluated mean costs and effects across treatment arms. NHB in each treatment arm and the incremental NHB were then estimated. In separate models, the seemingly unrelated regression method was also used to adjust cost and QALY models, in line with the statistical methods employed in the main ATLANTIS analysis.[16] This allows for simultaneous estimation of cost and QALY models, treating them as a single system, and accounts for correlations between the error terms in each model, leading to more efficient estimates. Results are provided for both complete case analysis and the full trial population using multiply imputed data.

The option for participants to continue trial medication beyond the initial 6-month randomised period introduced complexities for data analysis, with some participants opting to extend treatment to 12 months while others did not. This additional follow-up created potential biases for the estimation of treatments effects beyond 6 months, arising from patients being able to select into continuation of trial medication based on other factors, including their perception of benefit from it. To address these issues and mitigate the risk of

biased estimates due to varying follow-up lengths, we applied inverse probability weighting (IPW) methods, alongside more standard methods adopted in the main 6-month analysis. IPW adjusts for the probability of each participant continuing in the study based on observed characteristics, allowing for the generation of more robust and representative estimates of treatment effects across the extended timeframe.

Uncertainty around the ICER was determined using probabilistic sampling for the generation of 10,000 draws from the variance-covariance matrix for estimates of incremental costs and QALYs. A cost-effectiveness plane was used to illustrate the plotted estimates and the uncertainty surrounding the cost-effectiveness estimates.[33] The estimates of costs and QALYs were used to generate the probability of each treatment being cost-effective for different levels of cost-effectiveness thresholds. The results were presented using cost-effectiveness planes and cost-effectiveness acceptability curves. [34] Results of the evaluation were reported following the CHEERS criteria (Supplementary Table 3).[35] All analyses were carried out using Stata version 17.

**Patient and public involvement statement**

Patient and public involvement representatives were involved at all stages of the trial and provided valuable contributions to trial design, documentation, and outputs.

**Role of the funding source**

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**RESULTS**

Table 1 outlines the demographics and baseline characteristics for both the complete case population and the full analysis population and by treatment arm. The mean total cost in all participants in the complete case population at 6 months, including the cost of trial treatment, was £284. The total mean cost at 6 months was £291 in the placebo arm and £278 in the low-dose amitriptyline arm. Results were similar in the full analysis population.

Table 2 summarises regression analysis of cost-effectiveness outcomes using complete case analysis for the 6-month follow-up. Both adjusted and unadjusted analyses demonstrated relatively similar results. In the adjusted model, among 365 participants, there was an incremental cost difference of -£9.79 and a QALY difference of 0.0024, resulting in an ICER of -£4,089 per QALY, implying dominance of low-dose amitriptyline. The incremental NHB at the £20,000 threshold was 0.0029, with a 67.3% probability low-dose amitriptyline was cost-effective. Similarly, the unadjusted model showed dominance in 372 participants, with a cost difference of -£13.38, a QALY gain of 0.0035, and an ICER of -£3,863 per QALY. The NHB increased to 0.0041, and the probability of cost-effectiveness was 66.6%. At plausible ranges of the cost-effectiveness threshold, these probabilities remained relatively unchanged. Cost-effectiveness acceptability curves, unadjusted and adjusted for baseline characteristics, are provided in Supplementary Figures 1a and 1b. The cost-effectiveness plane adjusted for baseline characteristics is provided in Figure 1a, and the cost-effectiveness plane unadjusted for baseline characteristics in Supplementary Figure 1c. Cost-effectiveness results using multiple imputation data for the 6-month follow-up are provided in the online-only materials.

All complete case analyses at 12 months suggested that low-dose amitriptyline was more likely than not to be cost-effective at conventional thresholds (Table 3). This held for both unweighted and IPW analyses, and for adjusted and unadjusted analyses, with adjusted and IPW analyses providing the strongest evidence of both a gain in QALYs and a cost

saving. The adjusted IPW analysis in 224 participants demonstrated a reduction in costs of £66.59 and an increase in QALYs of 0.00594, leading to a dominant ICER of -£11,209 per QALY for low-dose amitriptyline. The NHB in the IPW-adjusted case was 0.00927, and the probability that low-dose amitriptyline was cost-effective was 84.7%. The comparison between the non-weighted and IPW results indicated minimal differences, suggesting that bias from discontinuation of trial medication was not substantial in this dataset. The relative consistency in ICERs, incremental costs, and QALYs between the weighted and non-weighted analyses further supported the robustness of the findings at 12 months. The cost-effectiveness plane adjusted for baseline characteristics for the complete case analysis at 12 months is provided in Figure 1b. All other cost-effectiveness acceptability curves and cost-effectiveness planes for these unadjusted and adjusted analyses are provided in Supplementary Figures 2a to 3d. Again, cost-effectiveness results using multiple imputation data for the 6-month follow-up are provided in the online-only materials.

## DISCUSSION

We conducted an economic evaluation of self-titrated, low-dose amitriptyline as a second-line treatment for IBS in primary care. Although the estimated incremental differences in costs and, particularly, QALYs were relatively small, results of our primary analysis at 6 months were ambiguous. At a willingness-to-pay threshold of either £20,000 or £30,000 per QALY gained, which is the general range of threshold values recommended by NICE, complete case analysis suggested that low-dose amitriptyline was more likely to be cost-effective than not, whereas multiple imputation analysis suggested it was more likely to be cost-ineffective than not. These results reflected the very small differences in QALYs and costs, with cost differences in both cases being less than £2 over 6 months.

The strength of evidence in terms of both NHB and probability of cost-effectiveness increased when accounting for the full trial follow-up duration of 12 months in those who chose to continue trial medication. The findings at 12 months reflect not only overall cost-effectiveness, as judged by conventional threshold-based analyses, but also suggest that low-dose amitriptyline represents a dominant option, offering higher QALYs at a reduced cost. Although participants had the option of discontinuing trial medication at 6 months, there is little evidence that this introduced bias arising from selection on observables that would imply overly optimistic evidence of cost-effectiveness from unadjusted estimates. IPW models, in all cases, exhibited minimal differences in our point estimates of NHB and the implied probability of cost-effectiveness. Indeed, in all cases, such differences were in a direction favourable to low-dose amitriptyline. It may be that the relatively short duration of 6 months of treatment with low-dose amitriptyline was insufficient to lead to a definite reduction in health care resource use or any substantial increase in quality of life, arising from its beneficial impact on symptoms of IBS,[16-18] but that with a longer duration of follow-up, both of these were more likely to occur, leading to an increased probability of cost-

effectiveness at 12 months. The probability of amitriptyline being cost-effective as a second-line treatment for IBS might increase further with a duration of treatment beyond 12 months but, as we did not perform economic modelling to assess whether this was the case, this is speculative.

The modest nature of QALY gains across analyses should be noted. This may reflect the complexity of assessing health utility changes in IBS management; the use of HRQoL measures based on the EQ-5D-3L questionnaire may not capture the nuanced impact of IBS symptoms on patients' quality of life fully, as it is not disease-specific. It may also reflect the difficulty in assessing health economic outcomes adequately in a trial powered, primarily, for symptom-based outcomes. Nevertheless, the findings suggest that low-dose amitriptyline, a low-cost intervention at £0.65 per 28 tablets, would lead to non-trivial cost savings when scaled to broader primary care settings and, when one considers that it is estimated that there are 2.3 million adults living with IBS in the UK,[5, 7] even if only a small proportion were suitable for low-dose amitriptyline, this would translate into large effects on cost savings and net health benefit. In addition, the cost-effectiveness of such an intervention may be better demonstrated when a longer time horizon is adopted. Incorporating decision-analytic models in future research could explore this issue further by extrapolating beyond the 12-month trial period, incorporating relevant longer-term factors, and confirming the long-term cost-effectiveness of low-dose amitriptyline. This would add further evidence to the findings of this cost-effectiveness analysis and offer more robust insights for policy and clinical decision-making. Finally, in secondary or tertiary care patients are likely to have more severe symptoms and management costs may be higher. The net gains per patient with amitriptyline use may, therefore, be greater although, again, this is hypothetical.

We are not aware of any other cost-effectiveness study of TCAs in IBS that uses trial level data, although there has been a previous decision analytic model performing a cost-

benefit analysis of various treatments for IBS-D.[36] These included licensed therapies, such as alosetron, eluxadoline, or rifaximin, a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, IBS-specific cognitive behavioural therapy, or the TCA desipramine. The analysis used clinical efficacy and tolerability data from a RCT of desipramine, in which the drug was titrated from 50mg o.d. to 150mg o.d.,[37] as well as Medicaid costs for a TCA. The authors reported that, from an insurer perspective, a TCA was the preferred treatment option below a willingness to pay threshold of $37,000 per QALY gained. However, the trial of desipramine recruited only females and not all patients had IBS, with 22% of participants having another disorder of gut-brain interaction.[37] In addition, the desipramine dose used in this RCT was in the ranges used to treat depression, which may have affected tolerability. Finally, the trial did not collect information on resource use.

In conclusion, in addition to the clinical benefit, safety, and acceptability of low-dose amitriptyline in patients with IBS found in the ATLANTIS trial, this analysis indicates this inexpensive medication is also likely to be cost-effective as a second-line treatment for IBS in primary care over 12 months. Although the cost-savings from amitriptyline in comparison with placebo were relatively small per person, NICE estimates that there are between 1.6 and 3.9 million consultations with a general practitioner with IBS symptoms per year in England and Wales.[38] This, together with the high prevalence of IBS globally,[5] suggests that even as a second-line treatment for IBS in primary care, amitriptyline could result in considerable health and cost benefits. This should strengthen recommendations from NICE,[9] and other organisations, to encourage general practitioners to offer it as a treatment option for people with ongoing IBS symptoms. Although there may be a reduction in referrals to secondary care with IBS due to increased uptake of an effective drug, in the future a greater proportion of patients seen in secondary care may have already tried amitriptyline, or another TCA, without experiencing any benefit. As a result, there may be an increase in utilisation of other

gut-brain neuromodulators, such as selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors, for which there is some evidence for efficacy in IBS, in this setting.[39] Greater use of combinations of gut-brain neuromodulators, termed augmentation,[40] may be required. Finally, this may serve as an impetus to increase access to brain-gut behavioural treatments for IBS, which are often reserved for patients with symptoms that are refractory to medical treatment, although most trials of these have not restricted their recruitment to this patient group.[41] Management guidelines for IBS in secondary care may, therefore, need to be updated.[42]

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**ETHICS COMMITTEE APPROVAL**

The final protocol and subsequent amendments were approved by Yorkshire and the Humber (Sheffield) Research Ethics Committee (19/YH/0150).

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**Table 1. Baseline demographics and characteristics of participants.**

| Characteristic | Complete case population | | | Full analysis population | | |
|---|---|---|---|---|---|---|
| | Low-dose amitriptyline (n = 186) | Placebo (n = 179) | All participants (n = 365) | Low-dose amitriptyline (n = 232) | Placebo (n = 231) | All participants (n = 463) |
| **Mean age (SD)** | 48.4 (15.2) | 48.0 (15.1) | 48.2 (15.1) | 49.2 (16.2) | 47.8 (15.9) | 48.5 (16.1) |
| **Female sex (%)** | 121 (65) | 120 (67) | 241 (66) | 156 (67) | 159 (69) | 315 (68) |
| **IBS subtype (%)** | | | | | | |
| IBS-C | 33 (18) | 28 (16) | 61 (17) | 40 (17) | 37 (16) | 77 (17) |
| IBS-D | 77 (41) | 72 (40) | 149 (41) | 92 (40) | 89 (39) | 181 (39) |
| IBS-M | 71 (38) | 74 (41) | 145 (40) | 93 (40) | 98 (42) | 191 (41) |
| IBS-U | 5 (3) | 5 (3) | 10 (3) | 7 (3) | 7 (3) | 14 (3) |
| **Recruitment hub (%)** | | | | | | |
| West Yorkshire | 31 (17) | 30 (17) | 61 (17) | 43 (19) | 44 (19) | 87 (19) |
| Southampton | 77 (41) | 79 (44) | 156 (43) | 92 (40) | 92 (40) | 184 (40) |
| West of England | 78 (42) | 70 (39) | 148 (41) | 97 (42) | 95 (41) | 192 (42) |
| **Mean baseline IBS-SSS (SD)*** | 269.2 (89.5) | 270.1 (89.3) | 269.7 (89.3) | 273.4 (90.5) | 272.1 (90.3) | 272.8 (90.3) |
| **Mean baseline PHQ-12 score (SD)*** | 6.2 (3.4) | 6.1 (3.5) | 6.2 (3.4) | 7.3 (4.3) | 7.7 (4.3) | 6.3 (3.5) |
| **Mean baseline HADS-depression score (SD)*** | 4.4 (3.8) | 4.1 (3.1) | 4.3 (3.5) | 4.4 (3.6) | 4.1 (3.2) | 4.3 (3.4) |
| **Mean baseline WSAS score (SD)*** | 11.3 (8.2) | 10.9 (6.9) | 11.1 (7.6) | 11.2 (8.2) | 11.5 (7.6) | 11.4 (7.9) |
| **Total cost in £UK (SD)** | | | | | | |
| Baseline | 199.0 (331.8) | 259.3 (1101.9) | 228.6 (806.6) | 201.2 (333.6) | 278.1 (1170.0) | 239.6 (860.2) |
| 1-3 months | 129.3 (303.8) | 149.1 (264.9) | 139.0 (285.2) | 130.6 (291.5) | 141.1 (250.9) | 135.8 (272.1) |
| 4-6 months | 140.1 (246.3) | 142.8 (240.0) | 141.4 (242.9) | 144.0 (263.5) | 137.4 (233.6) | 140.7 (249.0) |
| Total cost at 6 months (including treatment) | 278.0 (444.0) | 291.1 (419.0) | 284.4 (431.4) | 286.7 (455.5) | 284.5 (410.3) | 285.6 (433.5) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Mean EQ-5D-3L scores (SD)** | | | | | | |
| Baseline | 0.749 (0.220) | 0.751 (0.229) | 0.750 (0.224) | 0.748 (0.222) | 0.740 (0.236) | 0.744 (0.229) |
| 3 months | 0.819 (0.197) | 0.824 (0.183) | 0.821 (0.190) | 0.805 (0.217) | 0.825 (0.186) | 0.815 (0.203) |
| 6 months | 0.818 (0.187) | 0.794 (0.211) | 0.806 (0.200) | 0.815 (0.185) | 0.791 (0.216) | 0.803 (0.201) |
| **Mean QALYs gained at 6 months (SD)** | 0.401 (0.083) | 0.399 (0.082) | 0.400 (0.082) | 0.401 (0.082) | 0.398 (0.083) | 0.400 (0.083) |

*Lower scores are better.

**Table 2. Cost-effectiveness and net health benefit results at 6 months.**

| Analysis | Estimation method | Number of participants* | Difference in costs (£UK) | Difference in QALYs | ICER (£UK/QALY) | Incremental net health benefit at £20, 000 threshold | Probability of cost-effectiveness at £20, 000 threshold |
|---|---|---|---|---|---|---|---|
| Complete case analysis | Linear regression, unadjusted | 372 | -£13.38 | 0.0035 | -£3,863 (Dominant) | 0.0041 | 66.6% |
| | Linear regression, adjusted | 365 | -£9.79 | 0.0024 | -£4,089 (Dominant) | 0.0029 | 67.3% |
| Full analysis using multiple imputation | Linear regression, unadjusted | 463 | £0.19 | -0.00077 | -£241 (dominated) | -0.00078 | 45.6% |
| | Linear regression, adjusted | 463 | £1.59 | -0.00257 | -£639 (dominated) | -0.00257 | 33.0% |

*Numbers differ due to missingness on covariates that do not affect the unadjusted univariable regression.

**Table 3. Cost-effectiveness and net health benefit results at 12 months.**

| Analysis | Estimation method | Number of participants* | Difference in costs (£UK) | Difference in QALYs | ICER (£UK/QALY) | Incremental net health benefit at £20, 000 threshold | Probability of cost-effectiveness at £20, 000 threshold |
|---|---|---|---|---|---|---|---|
| Complete case analysis | Linear regression, unadjusted | 229 | -£43.28 | 0.00499 | -£8,676 (Dominant) | 0.00715 | 70.9% |
| | Linear regression, adjusted | 224 | -£48.65 | 0.00514 | -£9,463 (Dominant) | 0.00757 | 81.7% |
| | Linear regression unadjusted, with inverse probability weighting | 224 | -£59.11 | 0.00571 | -£10,348 (Dominant) | 0.00867 | 72.5% |
| | Linear regression adjusted, with inverse probability weighting | 224 | -£66.59 | 0.00594 | -£11,209 (Dominant) | 0.00927 | 84.7% |
| Full analysis using multiple imputation | Linear regression, unadjusted | 291 | -£74.76 | -0.00061 | £123,528 (bottom left, higher better) | 0.00313 | 58.3% |
| | Linear regression, adjusted | 291 | -£66.19 | 0.00057 | -£115,579 (dominant) | 0.00388 | 68.7% |
| | Linear regression, unadjusted with inverse probability weighting | 291 | -£86.29 | -0.00154 | £55,887 (bottom left, higher better) | 0.00277 | 55.9% |
| | Linear regression, adjusted with inverse probability weighting | 291 | -£85.29 | 0.00107 | -£79,810 (dominant) | 0.00533 | 72.6% |

*Numbers differ due to missingness on covariates that do not affect the unadjusted univariable regression. Such values also differ from tables relating to the analysis at 6 months due to only a proportion of the original cohort consenting to 12-month follow-up.

**Figure 1a. Cost-effectiveness plane using linear models adjusted for baseline characteristics for the complete case analysis at 6 months.**

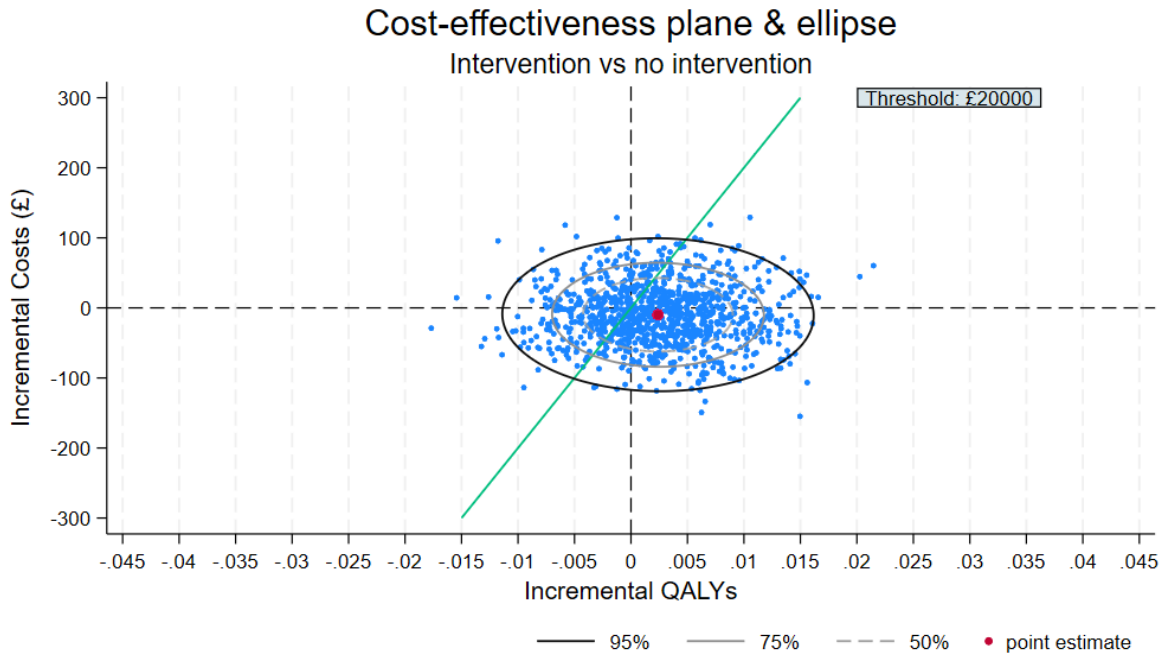

**Figure 1b. Cost-effectiveness plane using linear models adjusted for baseline characteristics for the complete case analysis at 12 months.**