Comparing Costs and Outcomes of Treatments for Irritable Bowel Syndrome With Diarrhea: Cost-Benefit Analysis

Eric D. Shah,[*] Jessica K. Salwen-Deremer,[*,‡] Peter R. Gibson,[§] Jane G. Muir,[§] Shanti Eswaran,[||] and William D. Chey[||]

*Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; ‡Department of Psychiatry, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; §Department of Gastroenterology, Central Clinical School, Monash University, Melbourne, Australia; and ||Division of Gastroenterology, Michigan Medicine, Ann Arbor, Michigan

BACKGROUND: **Irritable bowel syndrome (IBS) is one of the most expensive gastroenterological conditions and is an ideal target for developing a value-based care model. We assessed the comparative cost-benefit of treatments for IBS with diarrhea (IBS-D), the most common IBS subtype from insurer and patient perspectives.**

METHODS: **We constructed a decision analytic model assessing trade-offs among guideline-recommended and recently FDA-approved drugs, supplements, low FODMAP diet, cognitive behavioral therapy (CBT). Outcomes and costs were derived from systematic reviews of clinical trials and national databases. Health-gains were represented using quality-adjusted life years (QALY).**

RESULTS: **From an insurer perspective, on-label prescription drugs (rifaximin, eluxadoline, alosetron) were significantly more expensive than off-label treatments, low FODMAP, or CBT. Insurer treatment preferences were driven by average wholesale prescription drug prices and were not affected by health gains in sensitivity analysis within standard willingness-to-pay ranges up to $150,000/QALY-gained. From a patient perspective, prescription drug therapies and neuromodulators appeared preferable due to a reduction in lost wages due to IBS with effective therapy, and also considering out-of-pocket costs of low FODMAP food and out-of-pocket costs to attend CBT appointments. Comparative health outcomes exerted influence on treatment preferences from a patient perspective in cost-benefit analysis depending on a patients' willingness-to-pay threshold for additional health-gains, but health outcomes were less important than out-of-pocket costs at lower willingness-to-pay thresholds.**

CONCLUSIONS: **Costs are critical determinants of IBS treatment value to patients and insurers, but different costs drive patient and insurer treatment preferences. Divergent cost drivers appear to explain misalignment between patient and insurer IBS treatment preferences in practice.**

Keywords: Value; Value-Based Care; Economic Analysis; Markov; Pricing; QALY; Comparative Effectiveness; Coverage; ICER.

Irritable bowel syndrome (IBS) is a common condition in primary care and gastroenterology practice. It affects more than 30 million individuals in the United States[1,2] and accounts for more than 2 million annual office, inpatient, and emergency department visits.[3,4] IBS is subtyped by the predominant bowel habit of diarrhea or constipation, with diarrhea-predominant IBS (IBS-D) being the most common subtype.[1] Although incurable, IBS-D can be managed with over-the-counter remedies, prescription drugs, dietary interventions, or psychological interventions.[5,6] Several systematic reviews inform comparative clinical efficacy of IBS-D interventions,[7–11] but patients and providers lack information to compare relative cost and cost-effectiveness of potential treatment options. Without transparent information on the comparative costs and cost-effectiveness of treatment options, it is unsurprising that patients and clinicians often experience mutual frustration because of persistent barriers in starting or maintaining effective treatment.[12–14]

Abbreviations used in this paper: CBT, cognitive behavioral therapy; IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; ICER, incremental cost-effectiveness ratios; QALY, quality-adjusted life years; TCA, tricyclic antidepressants; WTP, willingness-to-pay.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2020.09.043

Cost increasingly poses a major hurdle to effective patient care in daily practice.[15-17] As patients take a more active role in their care, understanding the comparative costs of potential interventions is increasingly necessary in shared decision-making between patients and providers. Understanding cost is particularly important in chronic disease management.

Understanding the cost-effectiveness of IBS-D interventions is critical to enable patients and providers to identify high-value interventions for this common condition, and for gaining support from insurers, industry, and policymakers.[18,19] This study assesses the cost-effectiveness of interventions recommended in clinical practice guidelines for managing IBS-D.

What You Need to Know

Background

- Irritable bowel syndrome (IBS) is one of the most common and costly gastroenterological disorders in medicine.
- Diarrhea-predominant irritable bowel syndrome (IBS-D) is the most common IBS subtype.
- Physicians, patients, insurers, and policymakers need evidence on the comparative cost-benefit of IBS-D treatments.

Findings

- From an insurer perspective, tricyclic agents, low FODMAP, and CBT were preferred treatments, due to average wholesale prescription drug prices of rifaximin, eluxadoline, and alosetron.
- From a patient perspective, prescription drug therapies and neuromodulators appear preferable due to a reduction in lost wages due to IBS with effective therapy, and also considering out-of-pocket costs of low FODMAP food and out-of-pocket costs to attend CBT appointments.
- Health outcomes appear less important than out-of-pocket costs to patients at lower willingness-to-pay thresholds, but have increasing importance to patients at higher willingness-to-pay thresholds.

Implications for patient care

- By addressing specific cost-related barriers to treatment on a systems level, management of IBS in usual clinical practice can better align with outcomes reported in clinical trials.
- Cost discussions are imperative to fully address patients' needs in shared decision-making to choose the optimal IBS treatment.

Methods

We constructed a decision-analytic model to assess the quality of life and health care use associated with any single treatment for IBS-D. This study was conducted in accordance with the CHEERS checklist and recent guidelines for the conduct of cost-effectiveness analyses from the Second Panel on Cost-Effectiveness in Health and Medicine.[20,21] Treatments were recommended by either the most recent American Gastroenterological Association clinical practice guideline[6] or American College of Gastroenterology monograph,[5] or were Food and Drug Administration–approved for the management of IBS-D because publication of these documents were included. The specific design of each treatment regimen is outlined in the Supplementary Appendix (Supplementary Table 1).

Drugs and supplements were stratified into 2 analysis groups based on the quality of evidence for each therapy using GRADE methodology in the 2018 updated American College of Gastroenterology monograph[5]: at least moderate quality of supporting evidence, or low/very low quality of supporting evidence. Dietary and psychological interventions were included in both analyses to account for challenges in achieving a moderate quality-of-evidence rating in nondrug trials.[10]

Model Design

Our model design is outlined in Figure 1. The model assumed that individuals began treatment immediately and remained on treatment as long as safe and tolerated. Individuals were followed in 4-week cycles until the time horizon was reached or until 3 months after treatment was discontinued. A health state specific to an individual's current IBS symptom severity was assigned at the end of each 4-week cycle. Two health states (treatment response [ie, IBS in remission; "considerable relief of symptoms"] and treatment nonresponse [ie, active IBS; "lacking consideration relief of symptoms"]) were defined using the PROOF observational study, which followed a natural cohort of individuals meeting Rome III criteria for IBS receiving usual care (79% female gender, mean age of 43 [standard deviation, 15] years).[22] Incremental gains in health-related quality of life and costs were accumulated at the end of each treatment cycle. Analysis was performed using TreeAge Pro 2020 R2.2 (TreeAge Software Inc, Williamstown, MA).

Treatment Outcomes: Efficacy, Tolerability, and Safety

Our model accounted for major treatment-related properties including intolerable side effects leading to discontinuation, efficacy, and safety (Supplementary Table 2). We assumed that individuals experiencing intolerable side effects would discontinue treatment within the first 4-week cycle. Efficacy was used to define

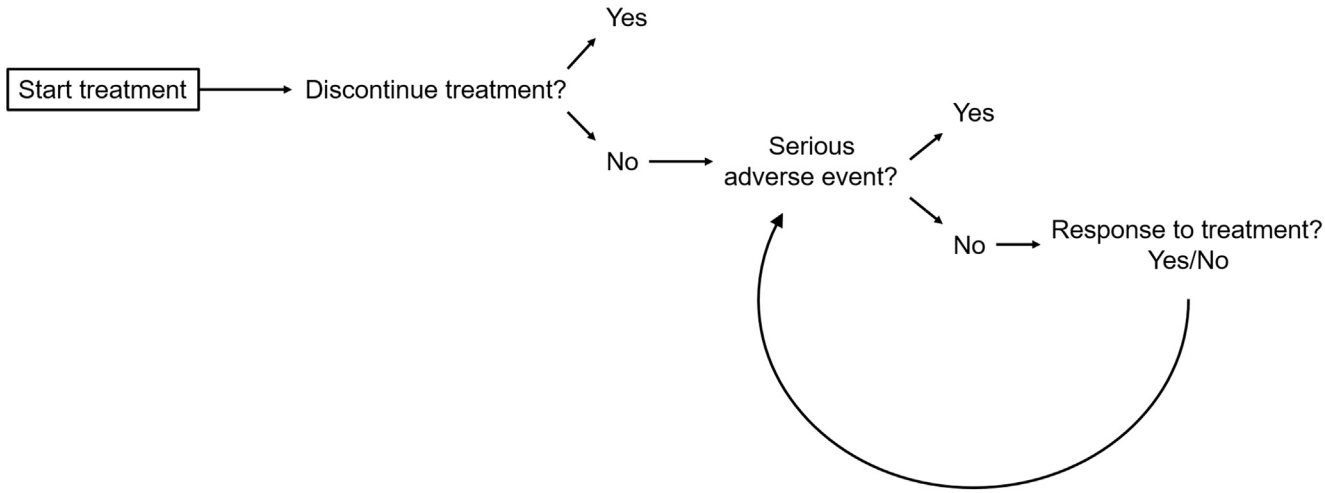


Figure 1. Model design.

the probability of treatment response, based on a global binary endpoint of adequate relief (ie, "do you feel adequate relief of symptoms?") in the active treatment arm of underlying clinical trials identified in recent network meta-analyses[23] and systematic reviews,[7,8,10] to account for placebo effect and patient expectations of therapy, which are important contributors to treatment effectiveness in clinical practice. Serious adverse events specified in Section 5 ("Warnings and Precautions") of relevant Food and Drug Administration labeling for drug interventions were modeled, specifically acute pancreatitis with eluxadoline therapy.[24]

Costs

Sources for health care cost data are reported in Supplementary Table 2. From an insurer perspective, individuals incurred direct costs related to drug treatment and incremental costs of outpatient and inpatient care based on rates of health care use among individuals with untreated IBS compared with healthy population norms. From a patient perspective, a standard set of nonmedical costs were included: out-of-pocket medical costs, work-productivity losses caused by treatment nonresponse, childcare related to receiving medical care, and transportation costs to medical visits. The societal perspective included all costs.

Quality of Life

Health-utility values were assigned to responder and nonresponder health states based on findings from the PROOF observational cohort using the multidimensional EuroQOL instrument.[22] Health utility values were used to generate quality-adjusted life years (QALY). The average QALY-gain over 1 year with untreated IBS or nonresponse to IBS therapy is 0.73, compared with an average QALY-gain over 1 year of 0.78 with response to IBS therapy.

Base-Case and Probabilistic Sensitivity Analysis

Base-case analysis was reported from societal, insurer, and patient perspectives in the US health care system to determine the incremental cost (2020 US dollars) and incremental effectiveness (QALY) referenced against an appropriate comparator. Incremental cost-effectiveness ratios (ICER) for each treatment modality were determined by dividing incremental cost by incremental effectiveness. We referenced incremental cost, incremental effectiveness, and ICER against "no therapy" if values exceeded zero.[25] We additionally referenced treatments against each other to compare cost-effectiveness among treatment interventions.

A conservative 1-year time horizon was used in base-case analysis, consistent with the time horizon for contemporary insurance coverage decisions (ie, annual enrollment periods) and the stability of outcome and cost estimates over this time period. A discount rate of 3% per annum discount rate was applied to costs and effectiveness outcomes.

Probabilistic sensitivity analysis was conducted using a Monte Carlo simulation of 10,000 trials to understand the impact of uncertainty in cost and outcome estimates on decision-making. Acceptability curves were constructed to evaluate the stability of cost-effective IBS-D treatment preferences at willingness-to-pay (WTP) levels per QALY ranging from $0 to $150,000/QALY-gained.

Additional Sensitivity Analyses

Budget-impact analysis with a 1-year time horizon was performed. One-way sensitivity analyses were conducted within the expected range of values for each outcome and QALY inputs in the model to assess model robustness. Additional sensitivity analyses were conducted to evaluate the effects of low FODMAP food costs,

mean daily wage, and severity of symptoms (ie, variable health gains and work productivity losses associated with treatment response) on treatment preference.

Results

Costs and Quality-Adjusted Life Years Associated With Untreated Irritable Bowel Syndrome With Diarrhea-Predominant

Receiving no treatment for IBS-D resulted in net costs of $6930.17 from a societal perspective, $2141.05 from an insurer perspective, and $4789.13 from a patient perspective (ie, out-of-pocket costs for all IBS-related expenditures including missed work and travel costs for repeated appointments) over a 1-year period, noting that these costs only included care directly related to IBS-D and increased health care use arising from having IBS-D compared with the general population. The QALY-gained from 1 year of untreated IBS-D was 0.73.

Four interventions supported by moderate-to-strong quality of evidence in clinical practice guidelines for the management of IBS-D were assessed: tricyclic antidepressants (TCA; rifaximin and eluxadoline), low FODMAP diet, and cognitive behavioral therapy (CBT).

Base-Case Analysis From an Insurer Perspective

Results from base-case analysis including costs, health gains (QALYs), and ICER (when appropriate) are reported in Table 1 for each intervention from societal, insurer, and patient perspectives (ie, all IBS-related out-of-pocket costs including missed work and travel costs to appointments). From an insurer perspective, TCA was the least expensive treatment option. Low FODMAP and CBT were more effective but more expensive than TCA (ICER = $35,902.94/QALY-gained for low FODMAP vs TCA; ICER = $890,709.41/QALY-gained for CBT vs low FODMAP) (Figure 2*A*). Compared with off-label, dietary, and behavioral interventions, rifaximin, eluxadoline, and alosetron were significantly more expensive than TCA; the ICER to choose alosetron over TCA required $6,290,826.13 in insurer expenses to gain 1 QALY.

Cost-effectiveness relationships among therapies were largely similar between societal and insurer perspectives.

Base-Case Analysis From a Patient Perspective

From a patient perspective, alosetron, eluxadoline, and TCA posed the lower out-of-pocket costs with differences in 1-year costs <$200 among these treatments (Table 1). Compared with the insurer perspective, the costs of low FODMAP and CBT were relatively higher from a patient perspective because of costs of low FODMAP food and because of time away from work and travel costs to attend CBT appointments (Figure 2*B*). As a result, low FODMAP and CBT were more effective but also more expensive than either eluxadoline or TCA. From a patient perspective, and in contrast to the insurer perspective, all treatments were more effective and less expensive than "no treatment."

Budget Impact Analysis

From an insurer perspective, low FODMAP, CBT, and TCA were all cost-saving compared with no treatment. TCA was the least costly treatment intervention at $964.07 per year, which includes all IBS-related health care costs borne by the insurer in addition to prescription drug costs. Treatment with low FODMAP or CBT cost an additional $278.55 or $844.88 per year compared with TCA, because of greater costs associated with health care providers for behavioral treatments. Treatment with rifaximin, eluxadoline, or alosetron was more expensive, costing an additional $5180.46 and $10,602.93 or $14,744.85 compared with TCA. Considering prescription drug costs, prescription drugs pose a 3- to 7-fold increase in health care expenditures compared with no treatment (ie, if insurance barriers prevent treatment access). In contrast, all treatment interventions resulted in cost savings compared with no treatment from a patient perspective because of more healthy days at work and less health care use. Prescription drugs were largely preferred from a patient perspective over low FODMAP and CBT from an out-of-pocket cost standpoint, but differences in costs among IBS treatments were more similar from a patient perspective than from an insurer perspective (Table 1).

Probabilistic Sensitivity Analysis

In probabilistic sensitivity analysis from an insurer perspective (Figure 3*A*), TCA was the preferred treatment below a WTP threshold of $37,000/QALY-gained. Low FODMAP was the preferred treatment above this threshold. CBT was preferred over rifaximin, eluxadoline, or alosetron. Rifaximin, eluxadoline, and alosetron were not preferred from an insurer perspective because of their average wholesale drug prices.

From a patient perspective considering out-of-pocket treatment costs, missed work, and travel costs for appointments (Figure 3*B*), alosetron was the preferred treatment strategy. Absent access to alosetron, eluxadoline was the preferred treatment strategy below a WTP threshold of $30,000/QALY-gained, whereas low FODMAP diet was the preferred treatment strategy above this WTP threshold. For individuals not appropriate for treatment with eluxadoline, TCA was the preferred treatment strategy below a WTP threshold of $30,000/QALY-gained, whereas low FODMAP was preferred above this threshold.

Table 1. Comparative Cost-Benefit of Low FODMAP Diet, CBT, and Drug Interventions Supported by Moderate to Strong Quality of Evidence

Strategy	Total cost ($/y)	Total effectiveness (QALY-gained)	Incremental cost ($)	Incremental effectiveness (QALY)	ICER ($/QALY-gain)
Societal perspective					
TCA	$3014.04	0.747	—	—	Reference
Low FODMAP	$3953.32	0.755	$939.28	0.008	$121,067.12/QALY-gained
CBT	$4469.35	0.756	$516.02	0.001	$811,591.30/QALY-gained
Alosetron	$17,576.95	0.758	$13,107.60	0.002	$6,290,826.13/QALY-gained
No treatment	$6930.17	0.730	—	—	Dominated by all treatments except alosetron
Rifaximin	$8870.45	0.749	—	—	Dominated by low FODMAP and CBT
Eluxadoline	$13,462.55	0.747	—	—	Dominated by low FODMAP and CBT
Insurer perspective					
TCA	$964.07	0.747	—	—	Reference
Low FODMAP	$1242.62	0.755	$278.55	0.008	$35,902.94/QALY-gained
CBT	$1808.95	0.756	$566.33	0.001	$890,709.41/QALY-gained
Alosetron	$15,708.92	0.758	$13,899.97	0.002	$6,671,115.74/QALY-gained
No treatment	$2141.05	0.730	—	—	Dominated by all treatments except alosetron
Rifaximin	$6144.53	0.749	—	—	Dominated by low FODMAP and CBT
Eluxadoline	$11,567.00	0.747	—	—	Dominated by low FODMAP and CBT
Patient perspective					
Alosetron	$1868.03	0.758	—	—	Reference
TCA	$2049.97	0.747	—	—	Dominated by alosetron
Low FODMAP	$2730.29	0.755	—	—	Dominated by alosetron
CBT	$2734.14	0.756	—	—	Dominated by alosetron
No treatment	$4789.13	0.730	—	—	Dominated by alosetron
Rifaximin	$2725.92	0.749	—	—	Dominated by alosetron
Eluxadoline	$1896.02	0.747	—	—	Dominated by alosetron

NOTE. QALYs-gained per year are rounded to the nearest thousandth in this table. Costs and ICERs are rounded to the nearest $0.01 in this table. ICER are rounded based on actual underlying values.
CBT, cognitive behavioral therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TCA, tricyclic antidepressant.

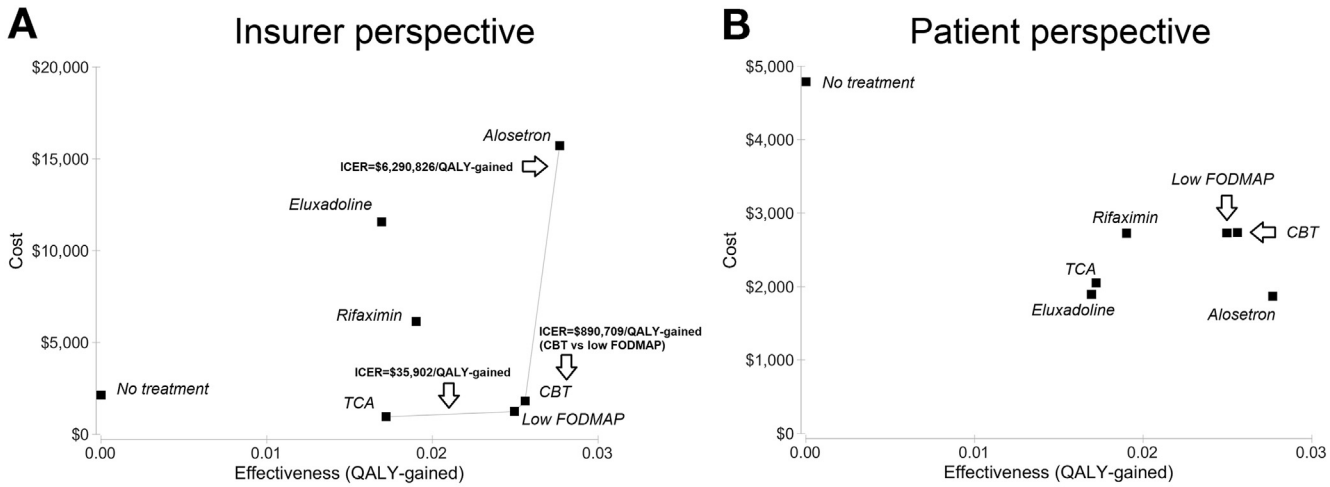


Figure 2. Cost-effectiveness plan showing the costs and QALYs of different treatments for IBS-D. (*A*) From an insurer perspective, TCA, low FODMAP, and CBT are low-cost options (*bottom right*), whereas prescription drugs represent higher-cost options. (*B*) In contrast, eluxadoline, TCA, and alosetron are lower cost from a patient perspective. Low FODMAP and CBT are higher cost from a patient perspective because of low FODMAP food costs and need for repeated CBT appointments. Health gains were similar on all IBS-D treatments (0.73–0.76 QALY-gained over 1 year).

Interventions Supported by Low/Very Low Quality-of-Evidence

Six interventions were assessed: (1) anticholinergic antispasmodics, (2) peppermint oil, (3) loperamide, (4) probiotics, (5) low FODMAP, and (6) CBT (Supplementary Figures 1–8). Considering the small size of underlying clinical trials, peppermint oil seemed more cost-effective than anticholinergic antispasmodics, loperamide, or probiotics from a patient perspective (Supplementary Figure 4). Peppermint oil was the least expensive treatment, followed by loperamide then anticholinergic antispasmodics followed by probiotics. Low FODMAP and CBT were more expensive than these treatment options (Supplementary Table 3).

Assessing Individual Determinants of Treatment Preferences by Insurers and Patients

In sensitivity analysis from an insurer perspective, preference toward off-label, dietary, and behavioral interventions was largely driven by prescription drug costs (Supplementary Figures 9–18). Particular to rifaximin, we assumed a 4-month retreatment interval based on TARGET 3 enrollment data; varying the retreatment interval between 10 weeks and 1 year did not significantly affect preference toward rifaximin at August 2020 average wholesale prices from an insurer perspective. Comparative health outcomes among IBS-D treatments did not significantly affect insurer treatment preferences in cost-benefit analysis.

From a patient perspective, preference toward prescription drugs was largely driven by a reduction in missed work because of effective prescription drug management (and loss of wages), weighed against increased costs of low FODMAP food or increased travel costs/childcare costs/missed work-days to attend CBT sessions or dietician follow-up appointments. In some cases, assumptions on comparative treatment outcomes (ie, comparative responder and discontinuation rates or the expected health gains with response to therapy [disease severity]) could change treatment preferences toward prescription drug treatments depending on a patient's WTP level to achieve health gains (Supplementary Figures 19–28).

Discussion

We conducted the first cost-benefit analysis to comparatively evaluate guideline-recommended IBS-D interventions from a societal perspective, and from insurer and patient perspectives relevant to general clinical practice. The insurer perspective is important to explore the rationale for insurance coverage decisions and prior authorizations. The patient perspective is critical to understand the importance of out-of-pocket expenses (including standard but nonobvious expenses, such as costs of food, travel costs to obtain health care, missed work to obtain health care, missed wages because of poorly controlled disease, and childcare costs to attend appointments), noting that nonobvious but measurable costs commonly drive treatment nonadherence in practice and lead patients to defer treatment for chronic health conditions, such as IBS.[26-28]

From an insurer perspective, TCA was the preferred treatment at low WTP thresholds in cost-benefit analysis and the preferred treatment in budget impact analysis, compared with behavioral interventions and drug interventions supported by at least a moderate level of evidence. Low FODMAP and CBT were preferred

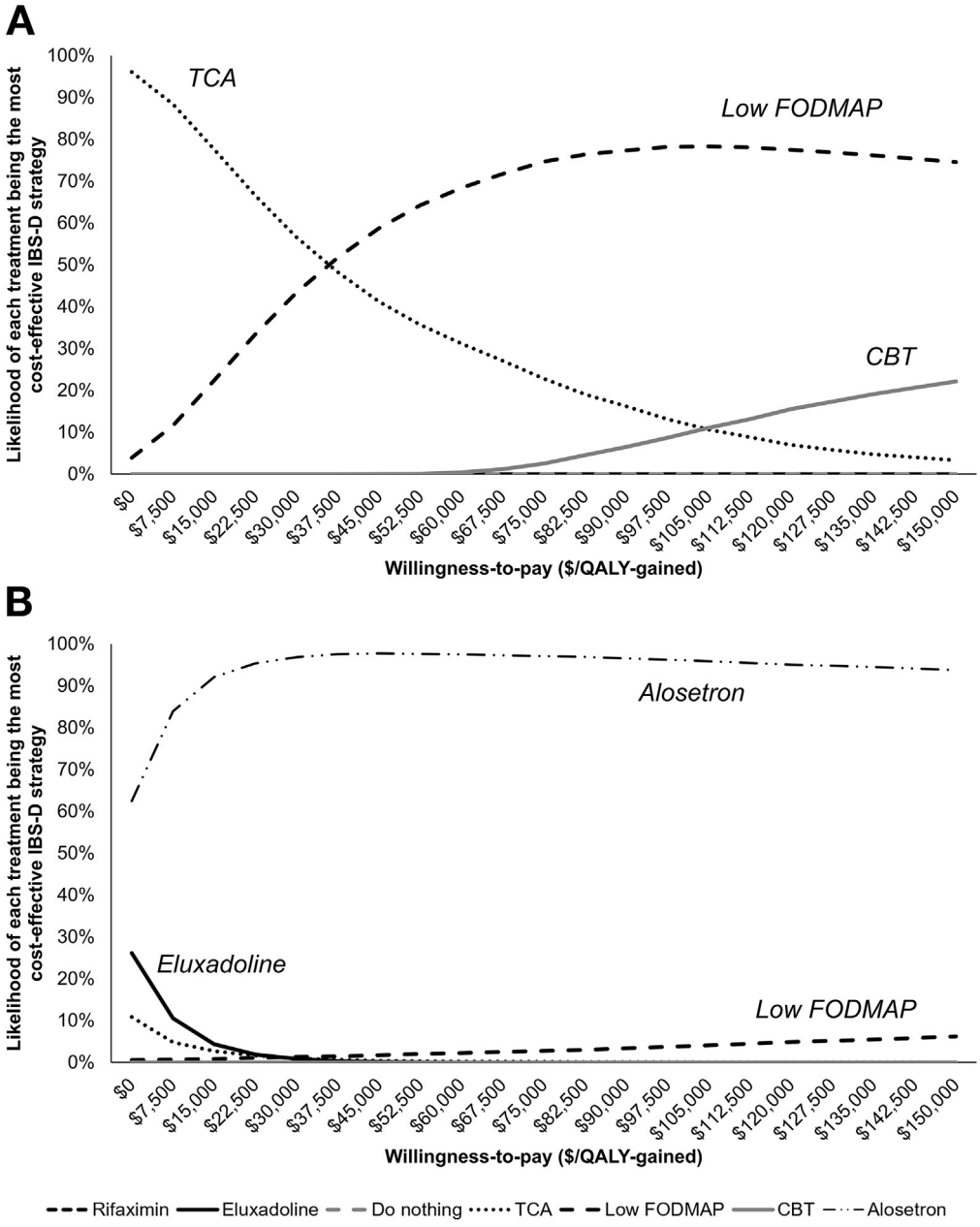


Figure 3. Cost-effectiveness acceptability curve showing the likelihood of cost-effectiveness of different treatments for IBS-D. (*A*) From an insurer perspective, TCA are preferred at lower willingness-to-pay thresholds to achieve additional health gains, whereas low FODMAP is preferred at higher willingness-to-pay thresholds. (*B*) In contrast, alosetron is preferred from a patient perspective regardless of willingness-to-pay threshold.

treatments at higher WTP thresholds in cost-benefit analysis from an insurer perspective. Rifaximin, eluxadoline, and alosetron were the most expensive treatments and were the least preferred interventions at current average wholesale prices. In contrast, from a patient perspective, prescription drug treatment with alosetron (or eluxadoline if alosetron was inappropriate) were the preferred treatments at lower WTP thresholds and in budget impact analysis. Low FODMAP was preferred at higher WTP thresholds. Regardless of perspective, low FODMAP and CBT had comparable costs and effectiveness gains, with treatment preference dependent on tradeoffs between cost of low FODMAP food and number of required psychologist visits. Among interventions with weak supporting evidence, peppermint oil and loperamide were preferred treatment options from a patient perspective on the basis of their relatively low cost.

We identified significant differences between insurers and patients as to which factors drive cost-effective shared decision-making. From an insurer perspective, treatment preferences were largely cost-driven rather than outcome-driven in sensitivity analysis. However, treatment preference are driven by more than direct drug costs, but also costs associated with health care use in IBS (explaining $964 in annual insurer costs to manage IBS on a TCA strategy despite $0.14/pill for amitriptyline). In contrast, other factors influence treatment preference from a patient perspective: How much does my IBS impact my ability to work? How effective is the treatment going to be? How often do I have to visit the doctor to complete treatment? Importantly, our

analysis suggests that comparative out-of-pocket costs to patients can vary significantly depending on their treatment choice—up to $866 over 1 year in our base-case analysis. Moreover, these patient-borne costs to manage IBS from a patient perspective are high, and the most effective treatment option only reduces annual total IBS-related out-of-pocket expenses to ~$1850 from a patient perspective. Our findings suggest that these nonobvious costs are important in patient-centered shared decision-making on appropriate IBS therapy and that costs should be discussed with patients, noting that cost discussions are underused in standard practice focused on comparative health outcomes alone.[27,29]

A major criticism of any cost-benefit analysis: in managing a nonlethal illness, would clinicians be willing to consider treatments with a lower evidence base (eg, neuromodulators, low FODMAP, and CBT) compared with on-label prescription drugs with higher costs? Although this question likely resonates with general gastroenterologists, cost-benefit analysis cannot methodologically account for this important question and ultimately cannot suggest that neuromodulators, low FODMAP, or CBT are any more effective than prescription drugs. Rather, this important question may be better addressed in future pragmatic clinical trials. Including neuromodulators, low FODMAP, and CBT in this analysis at least provides insight into how patients and gastroenterologists might make rational treatment decisions.[26] At the very least, our findings from insurer and patient perspectives provide insight into how costs might influence shared decision-making process at point-of-care and insurance coverage decisions in clinical practice.

Our results should be tailored to the needs of individual patients. Decision analytic models assume by design that all evaluated treatments are equally indicated. However, this is rarely the case in practice for 2 reasons. First, head-to-head trials evaluating competing treatments are lacking, and comparisons among clinical trial data are limited by variations in enrollment and study design. We addressed this limitation by defining response using a binary global symptom relief or adequate relief endpoint for at least 50% of the weeks in each underlying trial (when available), and by evaluating literature-derived ranges for each model input in sensitivity analysis. Second, individuals may have relative contraindications to specific treatments, which can reduce treatment efficacy, such as high baseline trait anxiety with CBT,[30] or could place an individual at risk for adverse events, such as patients with disordered eating behaviors undergoing a low FODMAP strategy.[31]

Our study design was limited to a 1-year time horizon, because long-term outcomes extending beyond 1 year are lacking in available clinical trial data. Additionally, IBS symptoms wax and wane significantly in long-term cohort studies.[22,32] Longer time horizons may also require consideration of understudied treatment-associated concerns raised in the literature, including antibiotic resistance with repeated use of antibiotics[33] or effects on intestinal flora or micronutrient deficiencies with long-term dietary interventions.[34] In clinical practice, periodic monitoring of disease activity/symptom relief, potential side effects, and treatment acceptability is required to determine the ongoing clinical indication for treatment and to make adjustments over time.

Despite the number of treatment options available for IBS, efficacy in a clinical trial setting is not the same as effectiveness in clinical practice. By addressing specific cost-related barriers to treatment on a systems level, effectiveness of IBS interventions in usual clinical practice might have a better opportunity to align with efficacy found in clinical trials.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.09.043.

References

1. Sperber AD, Dumitrascu D, Fukudo S, et al. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. Gut 2017;66:1075–1082.
2. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol 2012;10:712–721.
3. Buono JL, Mathur K, Averitt AJ, et al. Economic burden of irritable bowel syndrome with diarrhea: retrospective analysis of a U.S. commercially insured population. J Manag Care Spec Pharm 2017;23:453–460.
4. Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. Gastroenterology 2019;156:254–272.
5. Ford AC, Moayyedi P, Chey WD, et al. American College of Gastroenterology monograph on management of irritable bowel syndrome. Am J Gastroenterol 2018;113:1–18.
6. Weinberg DS, Smalley W, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology 2014;147:1146–1148.
7. Ford AC, Lacy BE, Harris LA, et al. Effect of antidepressants and psychological therapies in irritable bowel syndrome: an updated systematic review and meta-analysis. Am J Gastroenterol 2019;114:21–39.
8. Ford AC, Talley NJ, Spiegel BMR, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. BMJ 2008;337:a2313–a2313.
9. Menees SB, Maneerattannaporn M, Kim HM, et al. The efficacy and safety of rifaximin for the irritable bowel syndrome: a systematic review and meta-analysis. Am J Gastroenterol 2012;107:28–35.
10. Dionne J, Ford AC, Yuan Y, et al. A systematic review and meta-analysis evaluating the efficacy of a gluten-free diet and a low FODMAPs diet in treating symptoms of irritable bowel syndrome. Am J Gastroenterol 2018;113:1290–1300.

11. Shah E, Kim S, Chong K, et al. Evaluation of harm in the pharmacotherapy of irritable bowel syndrome. Am J Med 2012; 125:381–393.
12. Campbell JP, Burton E, Wymer S, et al. Out-of-pocket cost is a barrier to therapeutic drug monitoring in inflammatory bowel disease. Dig Dis Sci 2017;62:3336–3343.
13. Kennedy J, Wood EG. Medication costs and adherence of treatment before and after the Affordable Care Act: 1999–2015. Am J Public Health 2016;106:1804–1807.
14. Dabora MC, Turaga N, Schulman KA. Financing and distribution of pharmaceuticals in the United States. JAMA 2017;318:21.
15. Mehrotra A, Dean KM, Sinaiko AD, et al. Americans support price shopping for health care, but few actually seek out price information. Health Aff (Millwood) 2017;36:1392–1400.
16. Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for reform. JAMA 2016;316:858.
17. Shah ED, Chang L, Salwen-Deremer JK, et al. Contrasting clinician and insurer perspectives to managing irritable bowel syndrome: multilevel modeling analysis. Am J Gastroenterol https://doi.org/10.14309/ajg.0000000000000989. Epub ahead of print.
18. Neumann PJ, Cohen JT. Measuring the value of prescription drugs. N Engl J Med 2015;373:2595–2597.
19. Bach PB, Pearson SD. Payer and policy maker steps to support value-based pricing for drugs. JAMA 2015;314:2503.
20. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ 2013;346:f1049–f1049.
21. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. JAMA 2016;316:1093–1103.
22. Spiegel B, Harris L, Lucak S, et al. Developing valid and reliable health utilities in irritable bowel syndrome: results from the IBS PROOF cohort. Am J Gastroenterol 2009;104:1984–1991.
23. Black CJ, Burr NE, Camilleri M, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: systematic review and network meta-analysis. Gut 2019;69:74–82.
24. Cash BD, Lacy BE, Schoenfeld PS, et al. Safety of eluxadoline in patients with irritable bowel syndrome with diarrhea. Am J Gastroenterol 2017;112:365–374.
25. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000;17:479–500.
26. Shah ED, Siegel CA. Systems-based strategies to consider treatment costs in clinical practice. Clin Gastroenterol Hepatol 2020;18:1010–1014.
27. Perez SL, Weissman A, Read S, et al. U.S. internists' perspectives on discussing cost of care with patients: structured interviews and a survey. Ann Intern Med 2019;170:S39.
28. Gaines ME, Auleta AD, Berwick DM. Changing the game of prior authorization: the patient perspective. JAMA 2020; 323:705.
29. Shah ED, Ballou SK. Health economic studies are important for patients with irritable bowel syndrome and their gastroenterologists. Clin Gastroenterol Hepatol 2020: S1542356520306819.
30. Lackner JM, Jaccard J. Factors associated with efficacy of cognitive behavior therapy versus education for patients with irritable bowel syndrome. Clin Gastroenterol Hepatol 2019;17:1500–1508.
31. Hill P, Muir JG, Gibson PR. Controversies and recent developments of the low-FODMAP Diet. Gastroenterol Hepatol 2017;13:36–45.
32. El-Serag HB, Pilgrim P, Schoenfeld P. Systemic review: natural history of irritable bowel syndrome. Aliment Pharmacol Ther 2004;19:861–870.
33. Kothary V, Scherl EJ, Bosworth B, et al. Rifaximin resistance in *Escherichia coli* associated with inflammatory bowel disease correlates with prior rifaximin use, mutations in rpoB, and activity of Phe-Arg- -naphthylamide-inhibitable efflux pumps. Antimicrob Agents Chemother 2013;57:811–817.
34. Böhn L, Störsrud S, Liljebo T, et al. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. Gastroenterology 2015;149:1399–1407.

Reprint requests
Address requests for reprints to: Eric D. Shah, MD, MBA, Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, New Hampshire 03766. e-mail: eric.d.shah@hitchcock.org; fax: (603) 727-7925.

Conflicts of interest
These authors disclose the following: Peter R. Gibson has served as consultant or advisory board member for Atmo Biosciences, Allergan, Celgene, Janssen, MSD, Pfizer, Takeda, and Anatara; his institution has received speaking honoraria from Janssen, BMS, and Pfizer; and he has received research grants for investigator-driven studies from MSD and A2 Milk Company. William D. Chey is a consultant for Allergan, Biomerica, IM Health, Ironwood, Outpost, QOL Medical, Ritter, Salix, and Urovant; and has research grants from Commonwealth Diagnostics, Ironwood, QOL Medical, Salix, Urovant, Vibrant, and Zespri. Monash University financially benefits from the sales of a digital application, on-line educational course, and booklets on the FODMAP diet. The other authors disclose no conflicts.

Funding
Dr. Shah is supported by the AGA Research Foundation's 2019 AGA-Shire Research Scholar Award in Functional GI and Motility Disorders.

Supplementary Appendix

Model Assumptions Specific to Medical and Prescription Drug Coverage

Models from the insurer and patient perspective were developed under the assumption that a patient has a Health Management Organization managed care plan with a $0 copay and $0 annual premium, resulting in no charge for prescription drugs or provider visits to the patient (100% paid by the insurer). We did not analyze the variety of employer-sponsored high-deductible health plans and individual health plans available in the health care marketplace,[1] because higher cost-sharing by the patient (ie, higher deductibles, copays, and out-of-pocket maximums) would result in increasingly similar insurer- and patient-perspective findings.

Cost-Effectiveness and Budget-Impact of Drug/Supplement Interventions Supported by Low/Very Low Quality of Evidence, Low FODMAP, and CBT

Six interventions were assessed: (1) anticholinergic antispasmodics, (2) peppermint oil, (3) loperamide, (4) probiotics, (5) low FODMAP, and (6) CBT. Overall costs and QALYs are reported for each intervention (Supplementary Table 2). Each intervention was more effective and less costly than no treatment from societal, insurer, and patient perspectives.

From insurer and patient perspectives, peppermint oil and loperamide were more effective and less expensive than other treatments. Probiotics and anticholinergic antispasmodics were the least effective. Low FODMAP and CBT were the most expensive treatments but were more effective than probiotics and anticholinergic antispasmodics. Cost-effectiveness relationships among therapies were largely similar between societal and patient perspectives.

Budget impact analysis was performed from a patient perspective. All interventions were less costly to the patient than receiving no treatment. Peppermint oil was the least expensive intervention ($1799.15/year). Treatment with antispasmodics, loperamide, or probiotics respectively incurred incremental costs of $565.53, $635.64, and $1332.89 compared with peppermint oil. Low FODMAP ($3230.31/year) and CBT ($3275.79/year) were the most costly interventions.

In probabilistic sensitivity analysis, peppermint oil followed by loperamide were the most cost-effective treatment interventions across willingness-to-pay levels ranging from $0 to $150,000/QALY-gained from insurer and patient perspectives.

These findings varied significantly in sensitivity analysis on several model inputs, because of the weak quality of supporting evidence for underlying treatments (data not shown).

Comparison of Low FODMAP Diet and CBT

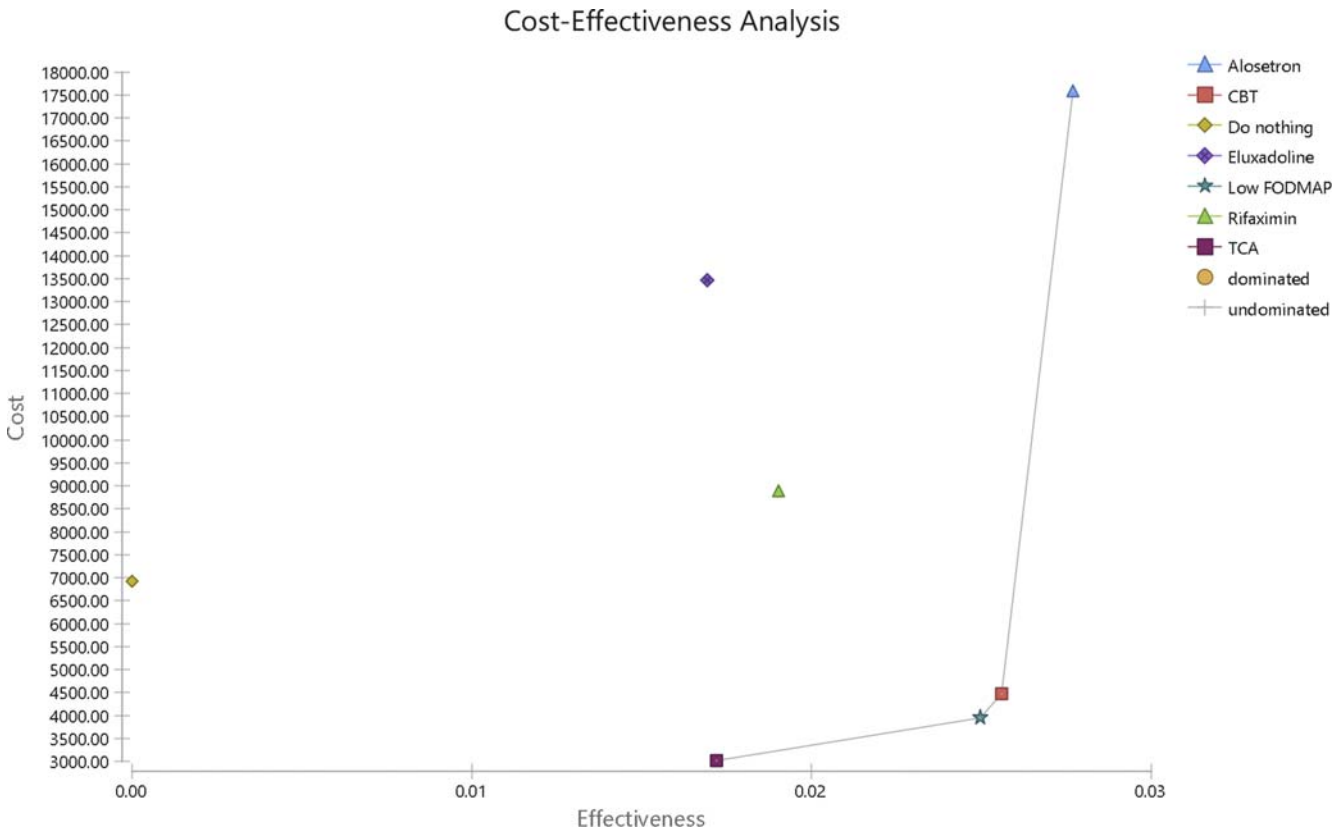
Low FODMAP and CBT had similar cost and health gains from a patient perspective, considering trade-offs between costs of low FODMAP food against the number of visits needed to complete CBT (influencing time away from work and travel costs to appointments). From an insurer perspective, CBT was more expensive because of the costs of repeated CBT sessions compared with fewer dietician appointments.

References

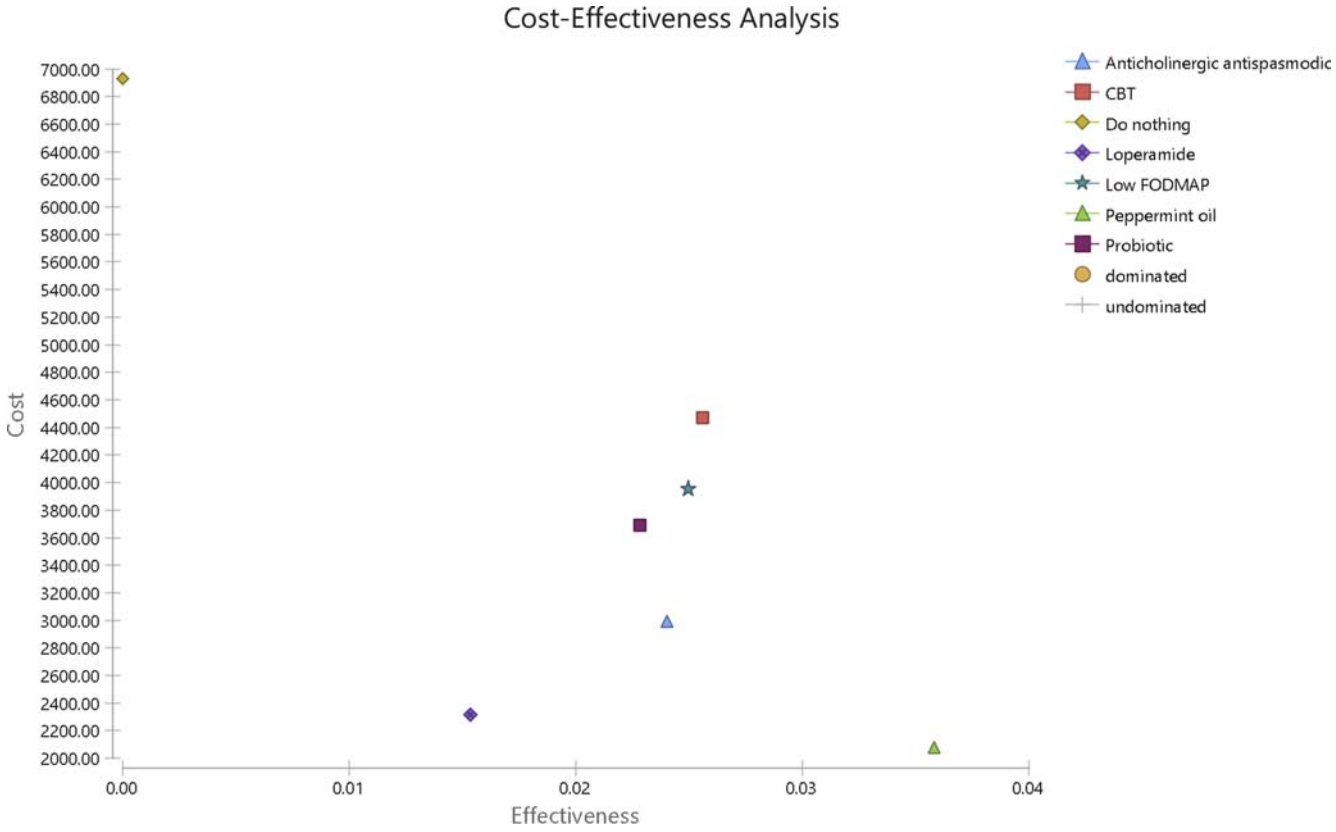
1. Ross JS. High-deductible health plans and higher-value decisions: a mirage or are we just not there yet? JAMA Intern Med 2016;176:397.
2. Eswaran SL, Chey WD, Han-Markey T, et al. A randomized controlled trial comparing the low FODMAP diet vs. modified NICE guidelines in US adults with IBS-D. Am J Gastroenterol 2016;111:1824–1832.
3. Ford AC, Quigley EMM, Lacy BE, et al. Efficacy of prebiotics, probiotics and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. Am J Gastroenterol 2014;109:1547–1561.
4. Ruepert L, Quartero AO, Wit NJ de, et al. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Database Syst Rev 2011;8:CD003460.
5. Ford AC, Lacy BE, Harris LA, et al. Effect of antidepressants and psychological therapies in irritable bowel syndrome: an updated systematic review and meta-analysis. Am J Gastroenterol 2019;114:21–39.
6. Black CJ, Burr NE, Camilleri M, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: systematic review and network meta-analysis. Gut 2020;69:74–82.
7. Food and Drug Administration. VIBERZI (eluxadoline) medical review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206940Orig1s000MedR.pdf.
8. Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. N Engl J Med 2016;374:242–253.
9. Cash BD, Lacy BE, Schoenfeld PS, et al. Safety of eluxadoline in patients with irritable bowel syndrome with diarrhea. Am J Gastroenterol 2017;112:365–374.
10. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011;364:22–32.
11. Lembo A, Pimentel M, Rao SS, et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome. Gastroenterology 2016;151:1113–1121.
12. Pimentel M, Morales W, Chua K, et al. Effects of rifaximin treatment and retreatment in nonconstipated IBS subjects. Dig Dis Sci 2011;56:2067–2072.
13. Drossman DA, Toner BB, Whitehead WE, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology 2003;125:19–31.
14. Dionne J, Ford AC, Yuan Y, et al. A systematic review and meta-analysis evaluating the efficacy of a gluten-free diet and a low

FODMAPs diet in treating symptoms of irritable bowel syndrome. Am J Gastroenterol 2018;113:1290–1300.

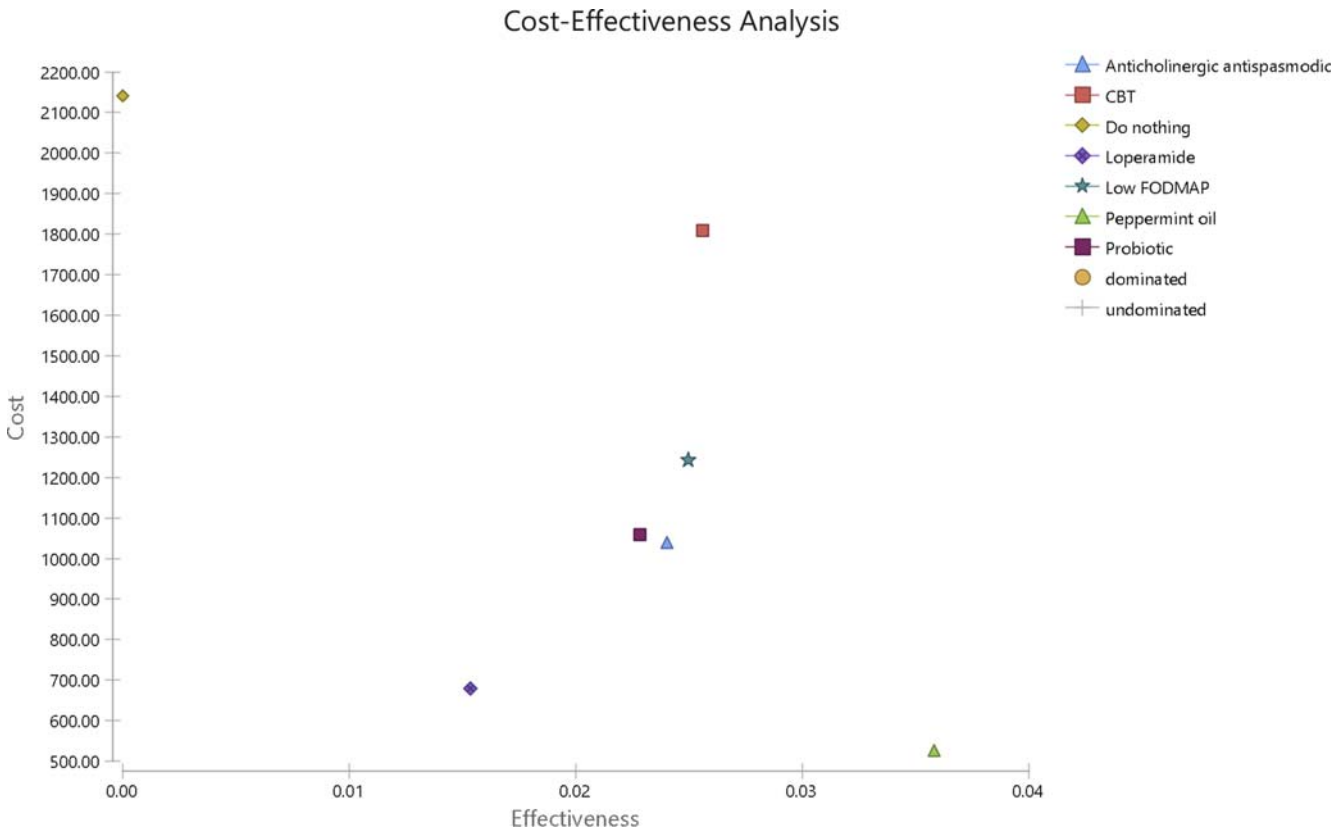
15. Lackner JM, Jaccard J, Keefer L, et al. Improvement in gastrointestinal symptoms after cognitive behavior therapy for refractory irritable bowel syndrome. Gastroenterology 2018; 155:47–57.
16. Page JG, Dirnberger GM. Treatment of the irritable bowel syndrome with Bentyl (dicyclomine hydrochloride). J Clin Gastroenterol 1981;3:153–156.
17. Ford AC, Talley NJ, Spiegel BMR, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. BMJ 2008;337:a2313–a2313.
18. Hovdenak N. Loperamide treatment of the irritable bowel syndrome. Scand J Gastroenterol Suppl 1987;130:81–84.
19. Lavö B, Stenstam M, Nielsen AL. Loperamide in treatment of irritable bowel syndrome: a double-blind placebo controlled study. Scand J Gastroenterol Suppl 1987;130:77–80.
20. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig Dis Sci 1993;38:1569–1580.
21. Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. Digestion 1999;60:77–81.
22. Hungin APS, Whorwell PJ, Tack J, et al. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther 2003;17:643–650.
23. Hungin APS, Chang L, Locke GR, et al. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. Aliment Pharmacol Ther 2005;21:1365–1375.
24. Buono JL, Carson RT, Flores NM. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. Health Qual Life Outcomes 2017;15:35.
25. Spiegel B, Harris L, Lucak S, et al. Developing valid and reliable health utilities in irritable bowel syndrome: results from the IBS PROOF cohort. Am J Gastroenterol 2009;104:1984–1991.
26. Medicaid. National Average Drug Acquisition Cost (NADAC) Database. Available at: https://data.medicaid.gov/.
27. Healthcare Bluebook. Available at: https://healthcarebluebook.com/page_ProcedureDetails.aspx?dataset=md&id=189&g=Electrocardiogram&directsearch=true.
28. Centers for Medicare & Medicaid Services. Physician fee schedule search. Available at: https://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx.
29. US Bureau of Labor Statistics. 2015 Consumer Expenditure Survey. Available at: https://www.bls.gov/cex/2015/combined/age.pdf.
30. Gearry RB, Irving PM, Barrett JS, et al. Reduction of dietary poorly absorbed short-chain carbohydrates (FODMAPs) improves abdominal symptoms in patients with inflammatory bowel disease: a pilot study. J Crohns Colitis 2009;3:8–14.
31. Amazon.com. IBGard 48 capsules. Available at: https://www.amazon.com/IBgard-IBgard%C2%AE-48-capsules/dp/B00Z7OIKXS.
32. Amazon.com. Align Extra Strength Probiotic. Available at: https://www.amazon.com/Align-Strength-Probiotic-Supplement-Digestive/dp/B07K98GCXM/ref=sr_1_1_s_it?s=hpc&ie=UTF8&qid=1548957504&sr=1-1-spons&keywords=align%2Bprobiotic&th=1.
33. US Bureau of Labor Statistics. Employment, hours, and earnings from the current employment statistics survey. Available at: https://data.bls.gov/timeseries/CES0500000003.
34. HCUPNet. Available at: https://www.ahrq.gov/cpi/about/otherwebsites/hcupnetquery/index.html.
35. US Census Bureau, Economics and Statistics Administration, US Department of Commerce. Households and Families: 2010. Available at: https://www.census.gov/prod/cen2010/briefs/c2010br-14.pdf.
36. Care.com, Inc. 2018 cost of care survey. Available at: https://www.care.com/c/stories/2423/how-much-does-child-care-cost/.
37. Muennig P. Cost-effectiveness analyses in health: a practical approach. 2nd ed. San Francisco: Jossey-Bass, 2008.
38. Buono JL, Mathur K, Averitt AJ, et al. Economic burden of irritable bowel syndrome with diarrhea: retrospective analysis of a U.S. commercially insured population. J Manag Care Spec Pharm 2017;23:453–460.



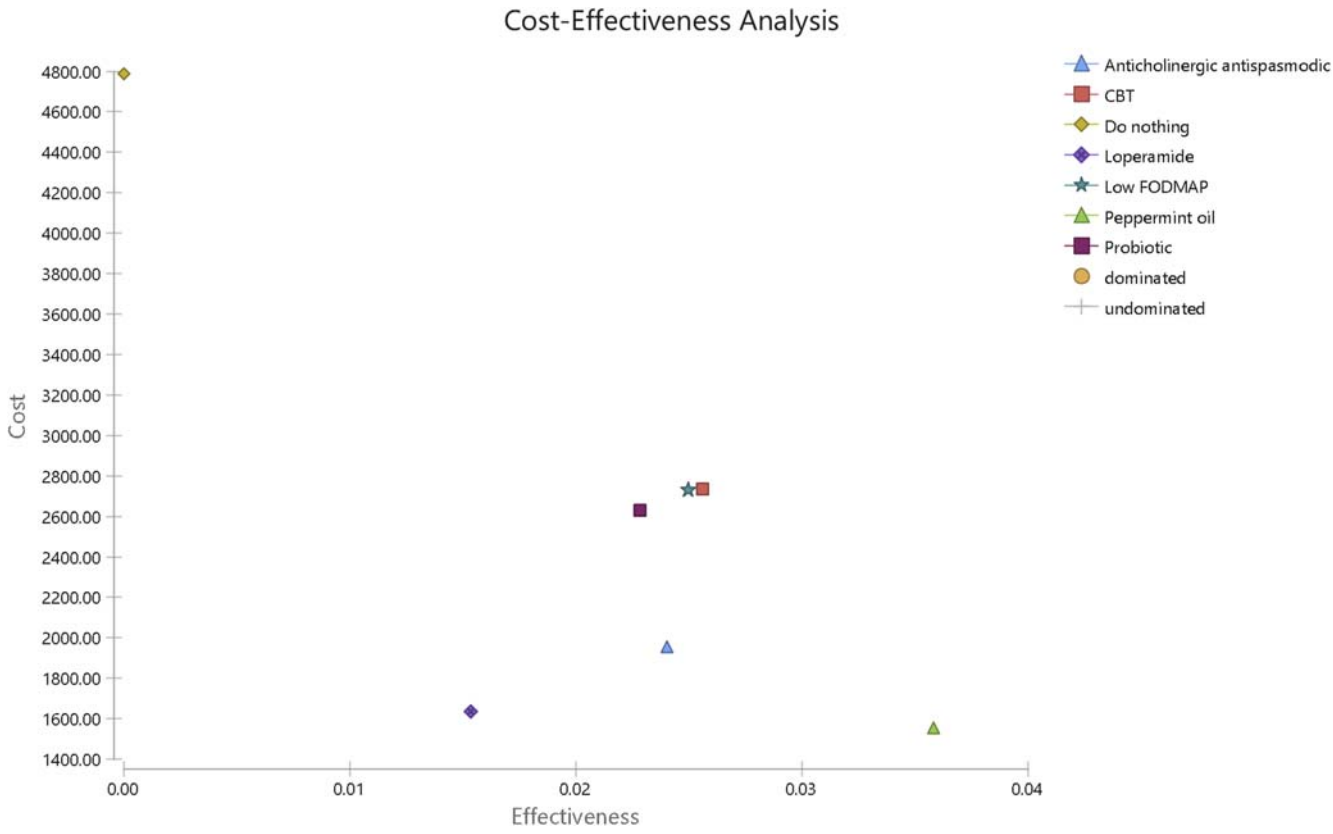
Supplementary Figure 1. Cost effectiveness of low FODMAP, CBT, and drug/supplement interventions supported by moderate to strong evidence from a societal perspective.



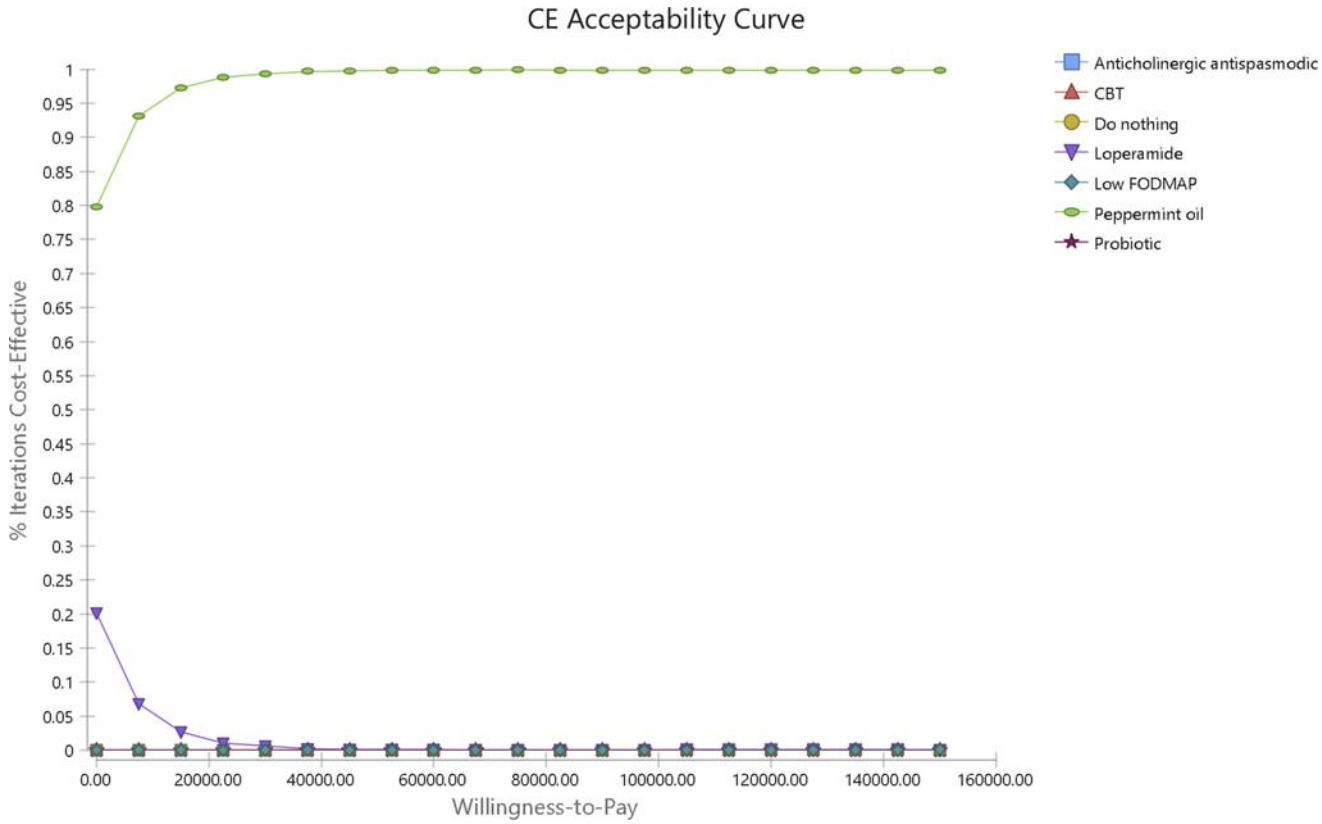
Supplementary Figure 2. Cost effectiveness of low FODMAP, CBT, and drug/supplement interventions supported by low/very low evidence from a societal perspective.



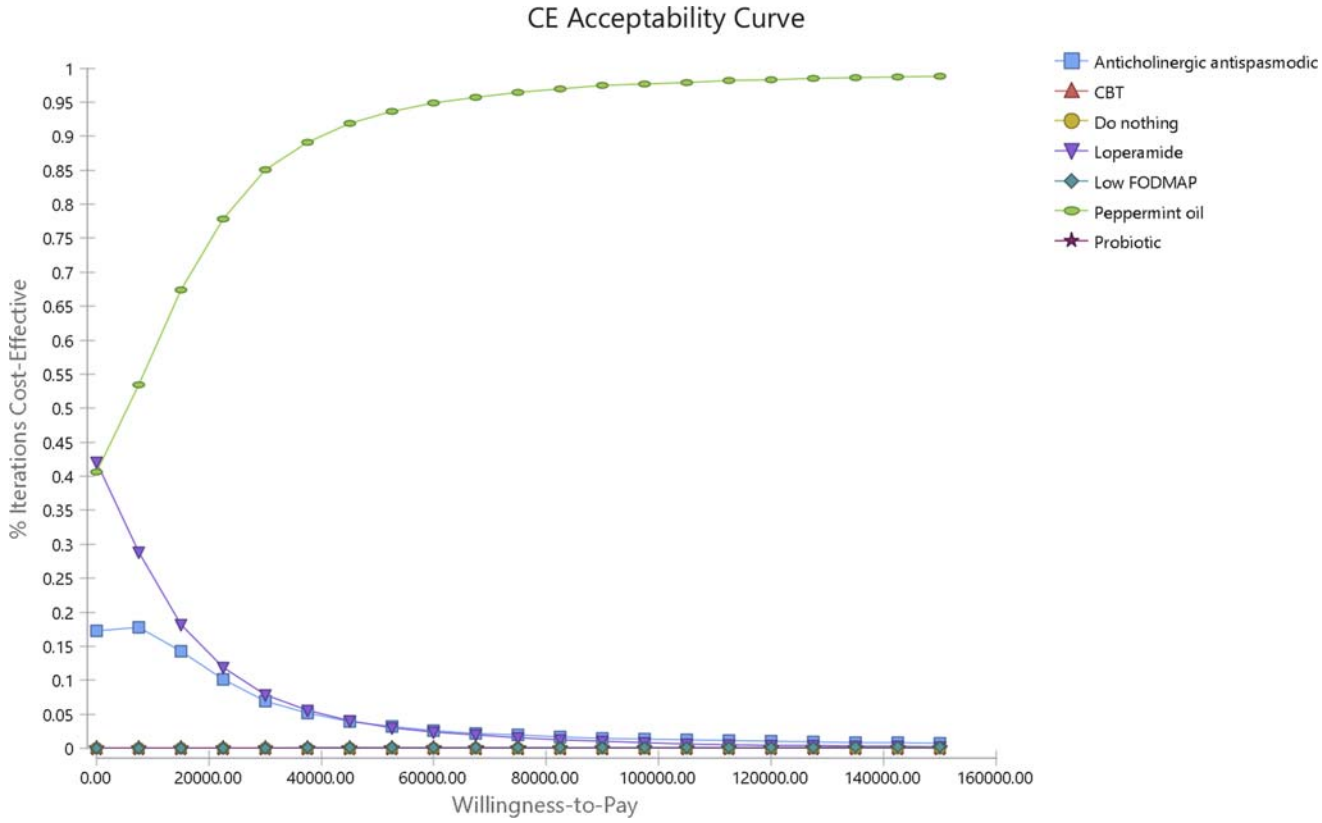
Supplementary Figure 3. Cost effectiveness of low FODMAP, CBT, and drug/supplement interventions supported by low/very low evidence from an insurer perspective.



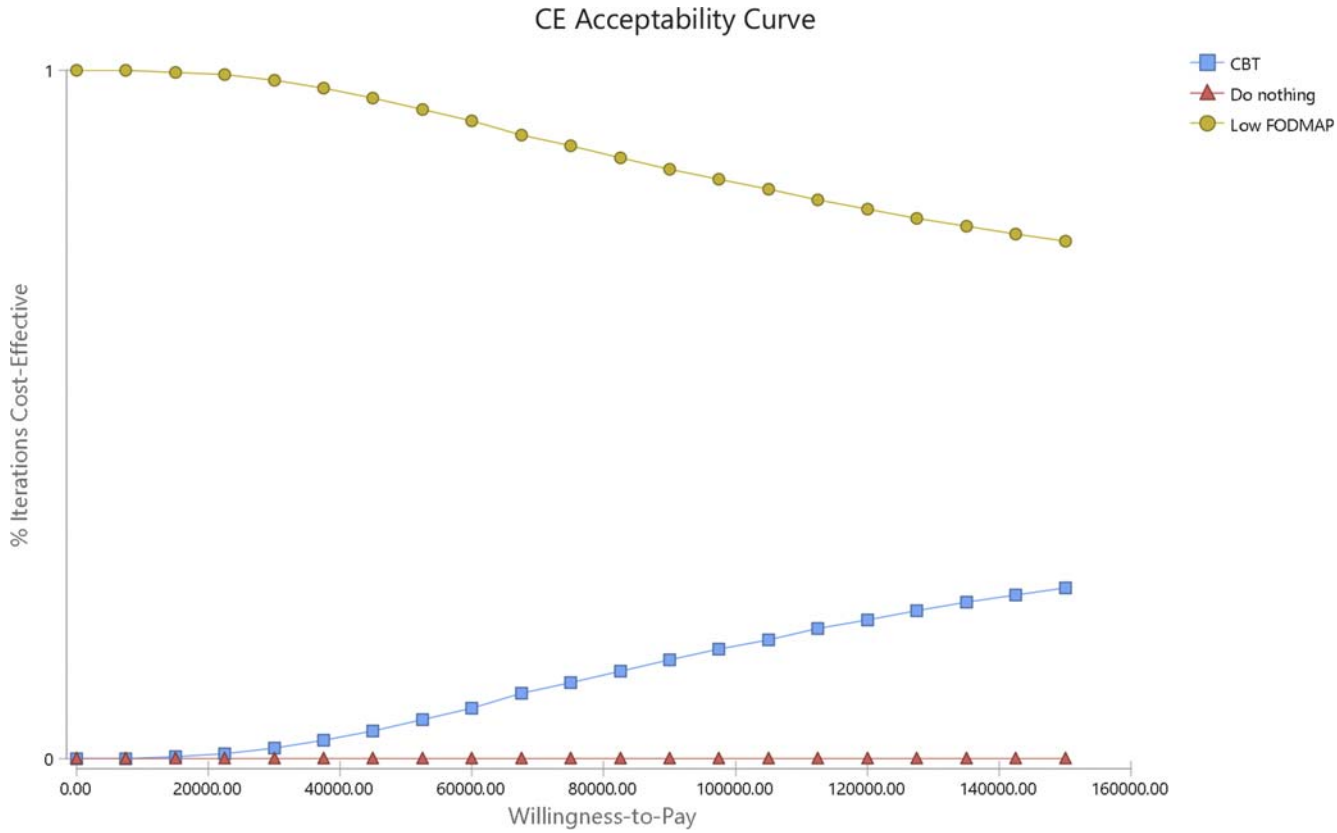
Supplementary Figure 4. Cost effectiveness of low FODMAP, CBT, and drug/supplement interventions supported by low/very low evidence from a patient perspective.



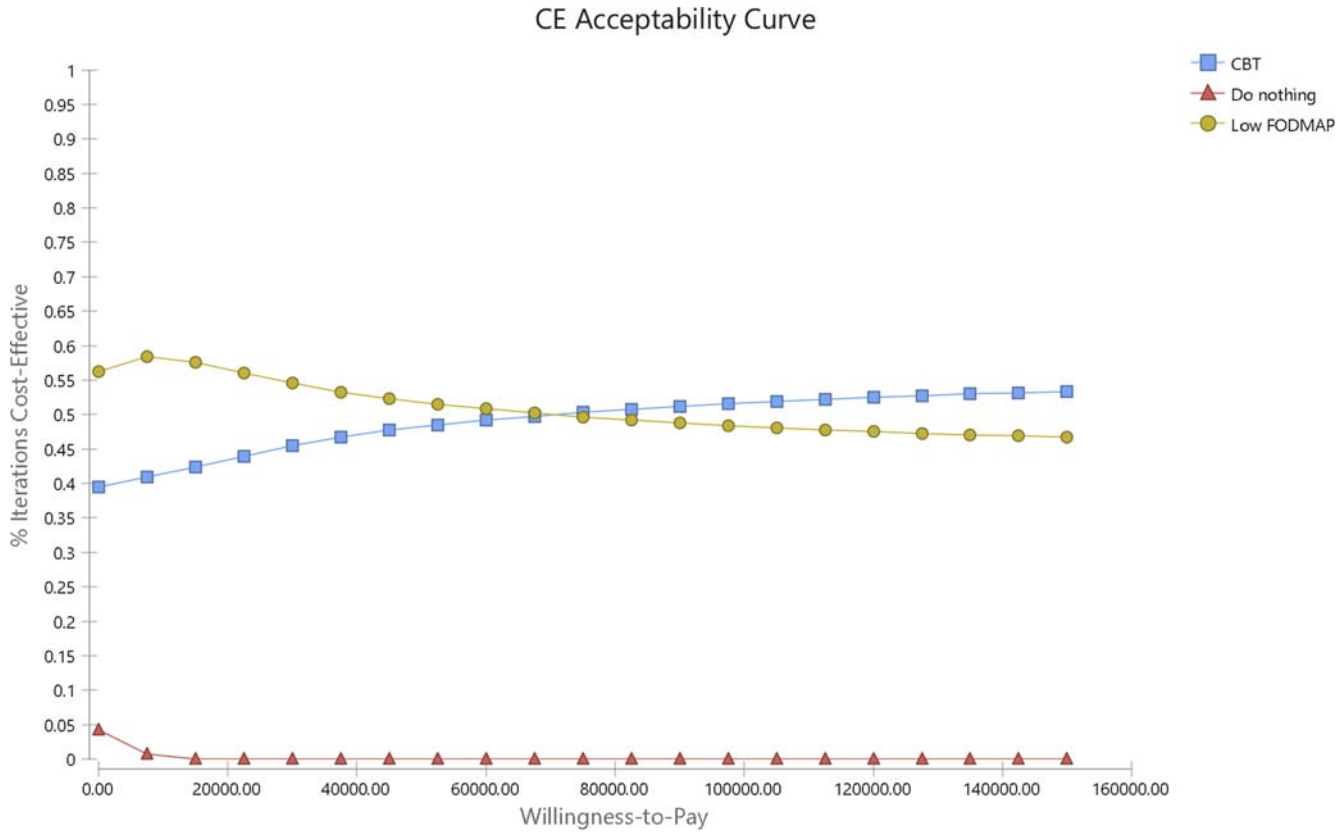
Supplementary Figure 5. Acceptability curves of low FODMAP, CBT, and drug/supplement interventions supported by low/very low quality of evidence from an insurer perspective. The probability of each therapy being the most cost-effective treatment strategy is represented along the vertical axis, based on the WTP per QALY gained. CE, cost effectiveness.



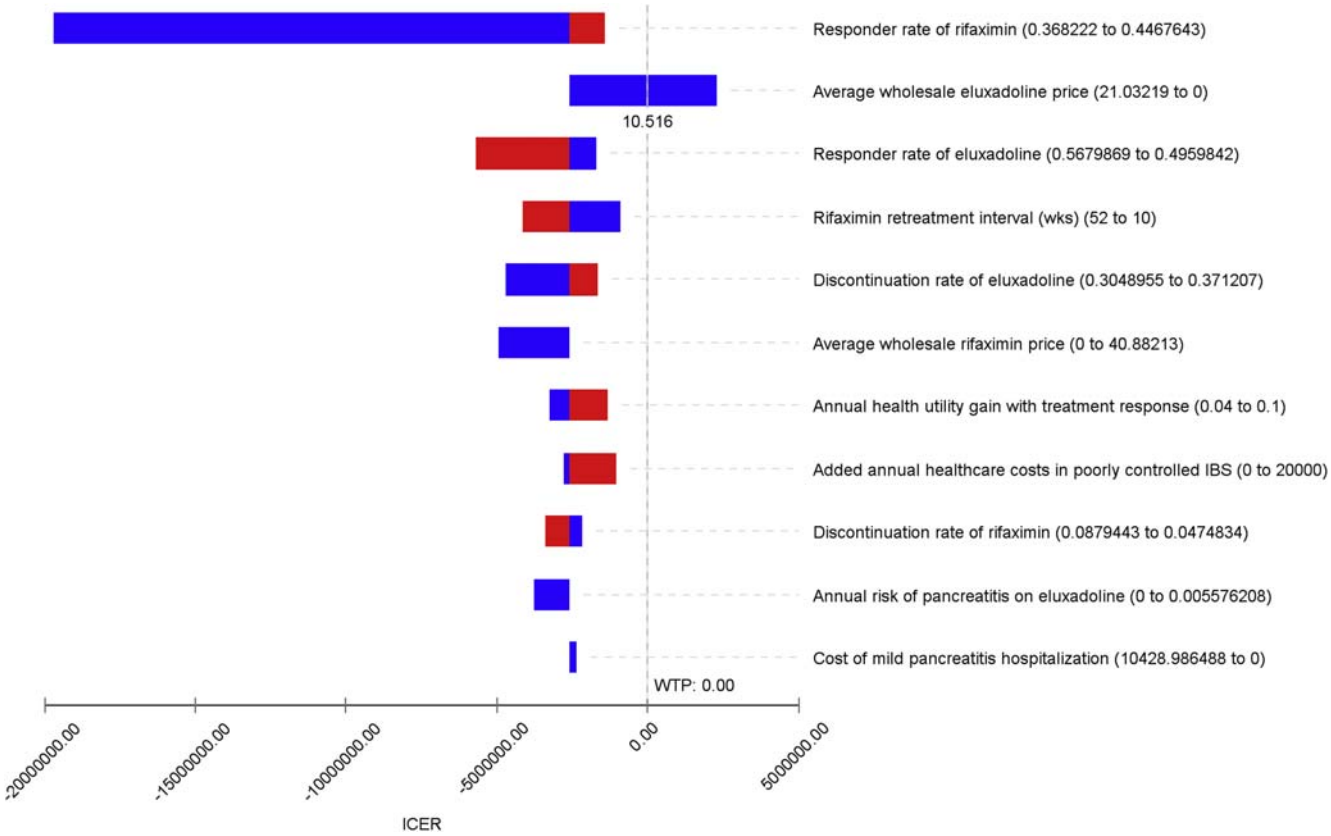
Supplementary Figure 6. Acceptability curves of low FODMAP, CBT, and drug/supplement interventions supported by low/very low quality of evidence from a patient perspective. The probability of each therapy being the most cost-effective treatment strategy is represented along the vertical axis, based on the WTP per QALY gained. CE, cost effectiveness.



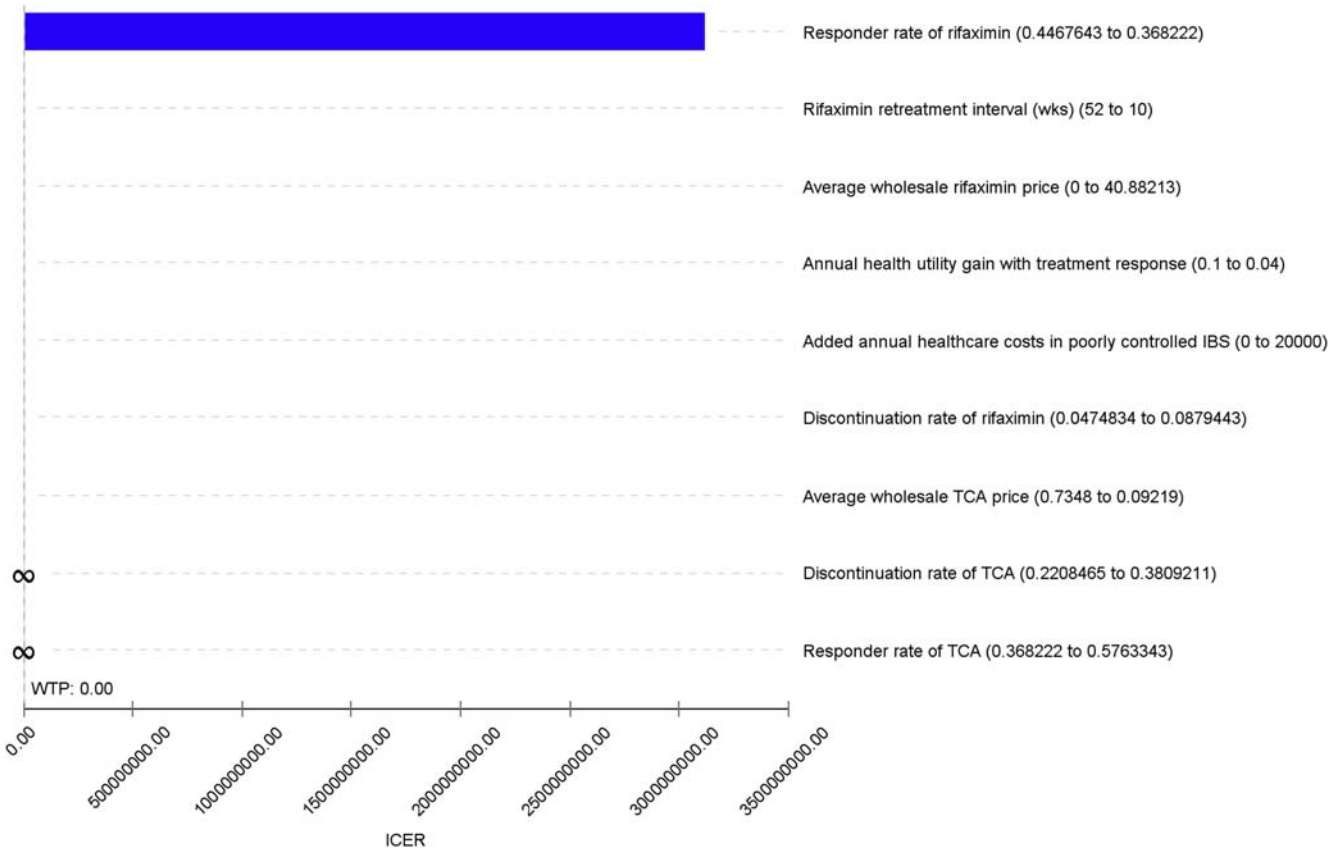
Supplementary Figure 7. Acceptability curves of low FODMAP and CBT from an insurer perspective. The probability of each therapy being the most cost-effective treatment strategy is represented along the vertical axis, based on the WTP per QALY gained. CE, cost effectiveness.



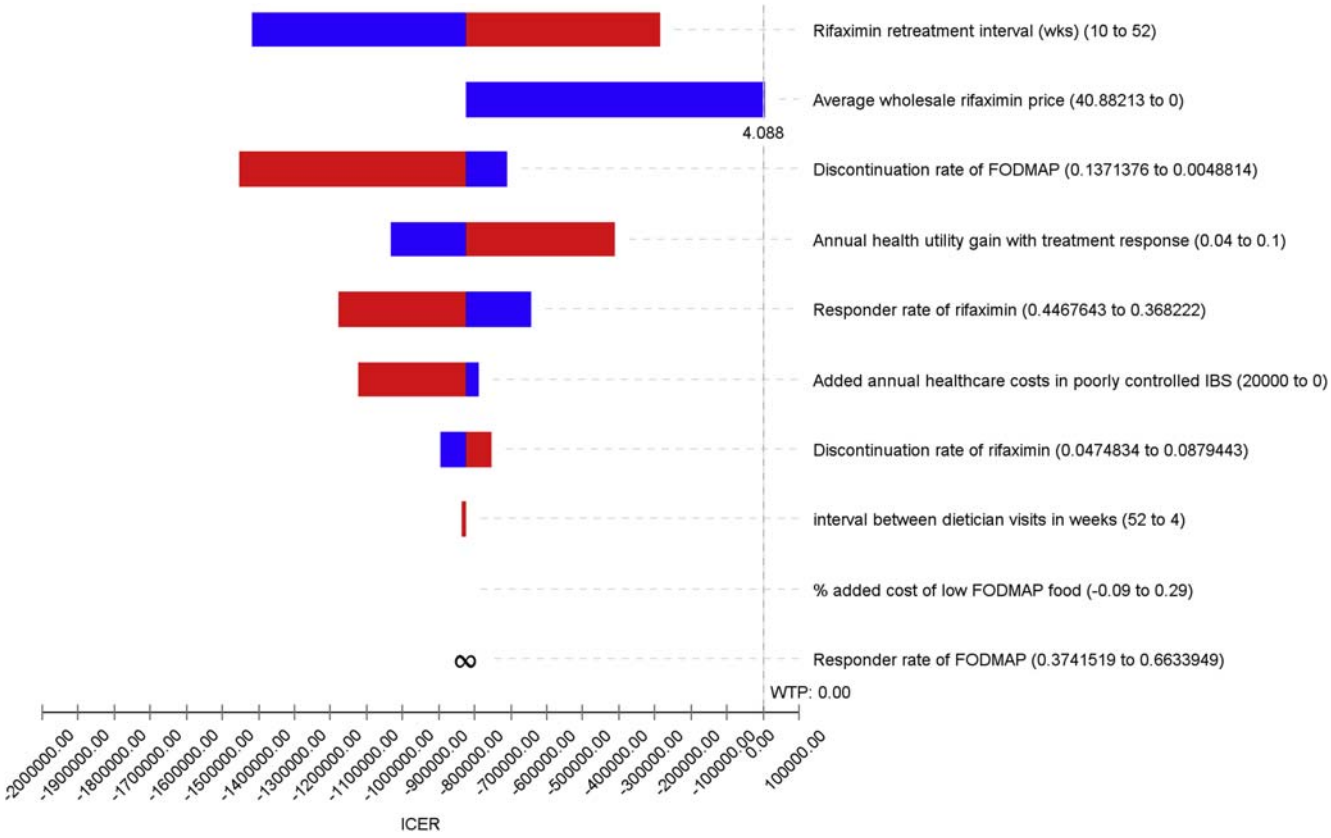
Supplementary Figure 8. Acceptability curves of low FODMAP and CBT from a patient perspective. The probability of each therapy being the most cost-effective treatment strategy is represented along the vertical axis, based on the WTP per QALY gained. Low FODMAP was preferred below a WTP of $70,000/QALY gained, whereas CBT was preferred above this threshold. CE, cost effectiveness.



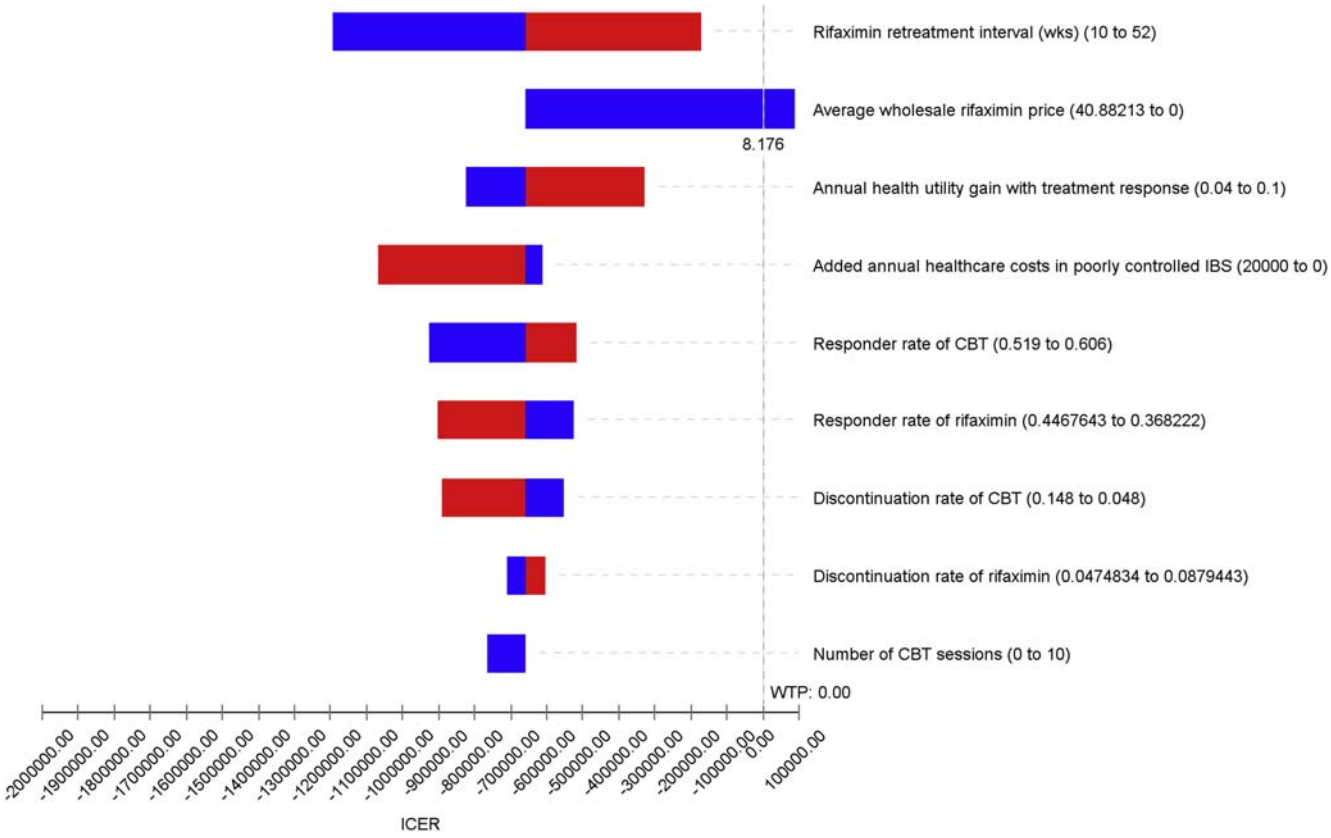
Supplementary Figure 9. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of rifaximin compared with eluxadoline from an insurer perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for rifaximin referenced against eluxadoline, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. Rifaximin dominated eluxadoline (ie, rifaximin was more effective and less expensive) across the range of model inputs, unless the average wholesale price of eluxadoline was below $10.52 per pill.



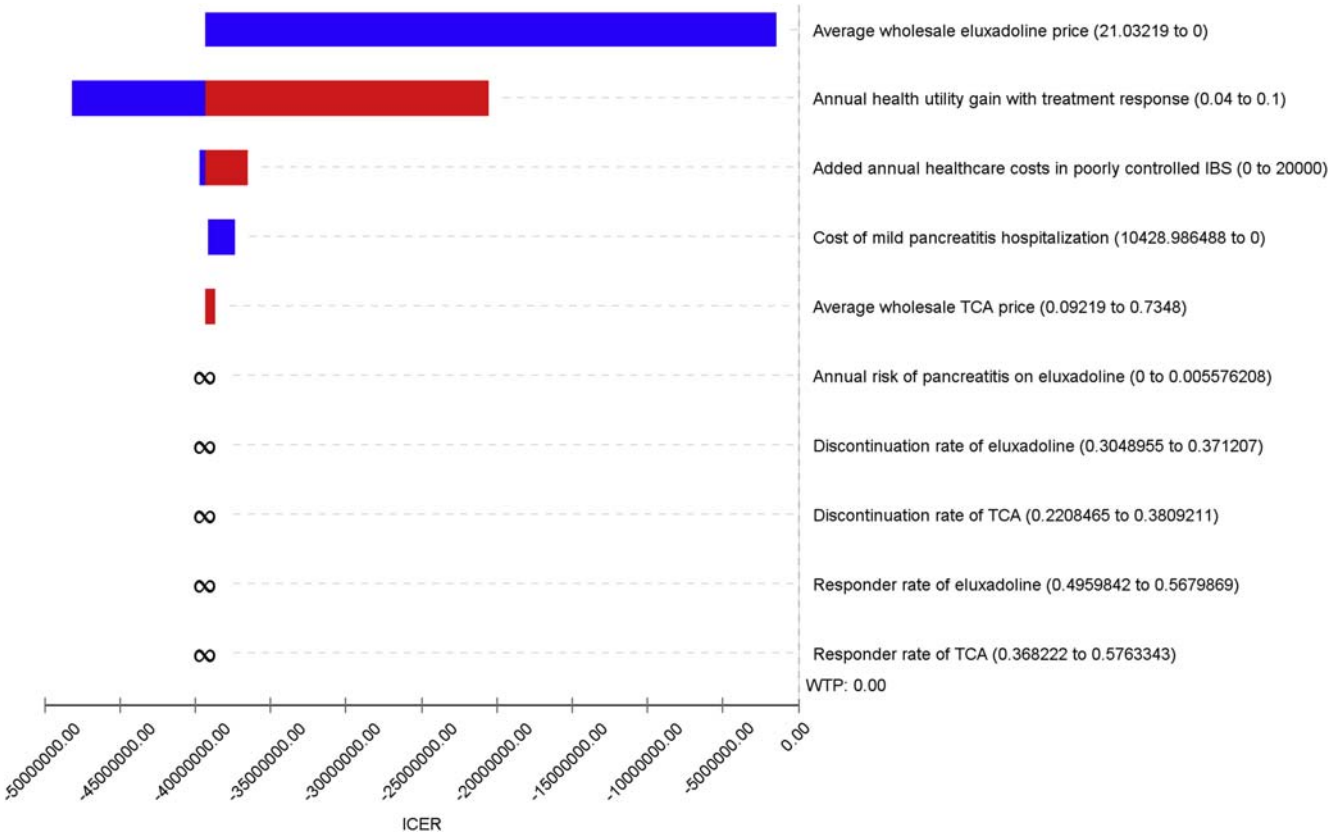
Supplementary Figure 10. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of rifaximin compared with TCA from an insurer perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for rifaximin referenced against TCA, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. Rifaximin remains more effective but more expensive across the range of model inputs.



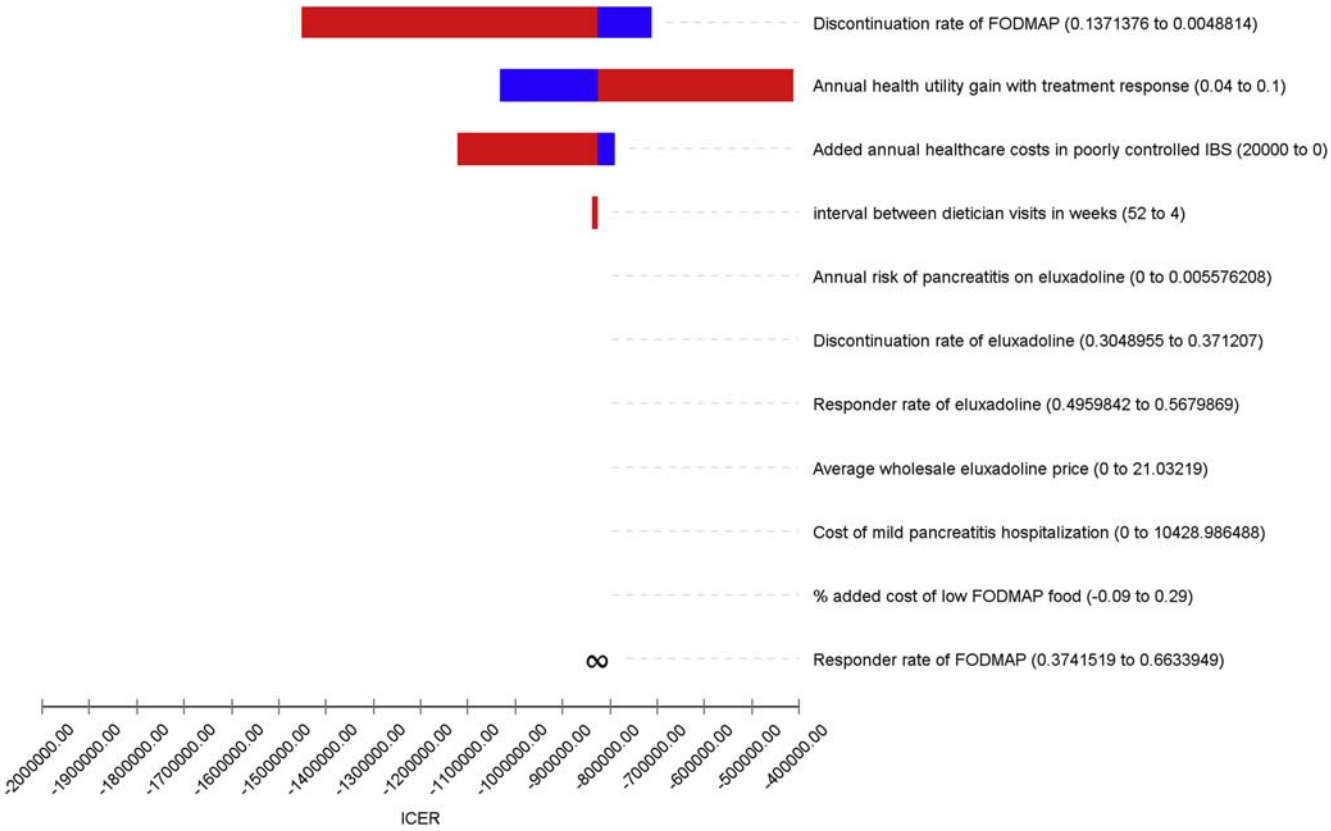
Supplementary Figure 11. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of rifaximin compared with low FODMAP from an insurer perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for rifaximin referenced against low FODMAP, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. Low FODMAP remains more effective and less expensive across the range of model inputs, unless the average wholesale price of rifaximin was below $4.09 per pill.



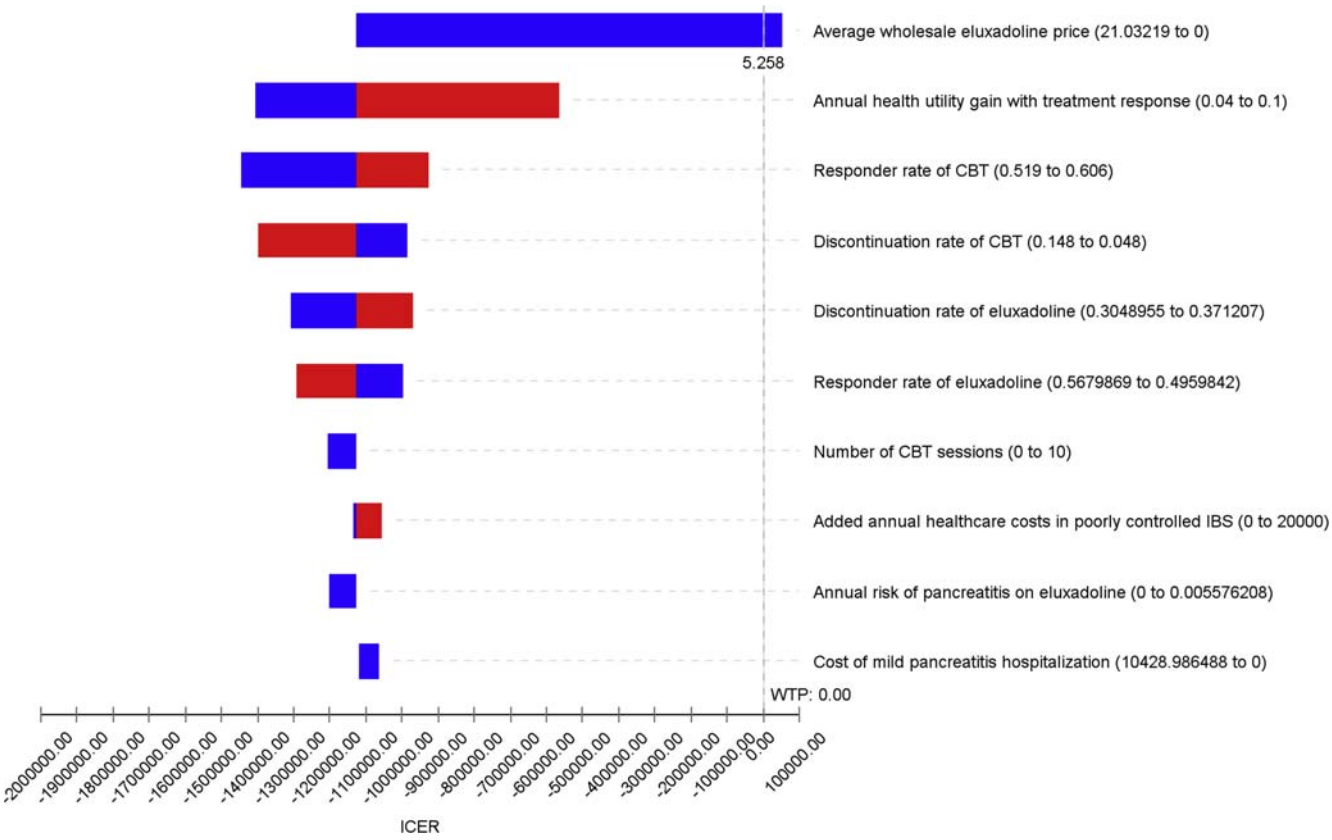
Supplementary Figure 12. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of rifaximin compared with CBT from an insurer perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for rifaximin referenced against CBT, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. CBT remains more effective and less expensive across the range of model inputs, unless the average wholesale price of rifaximin was below $8.18 per pill.



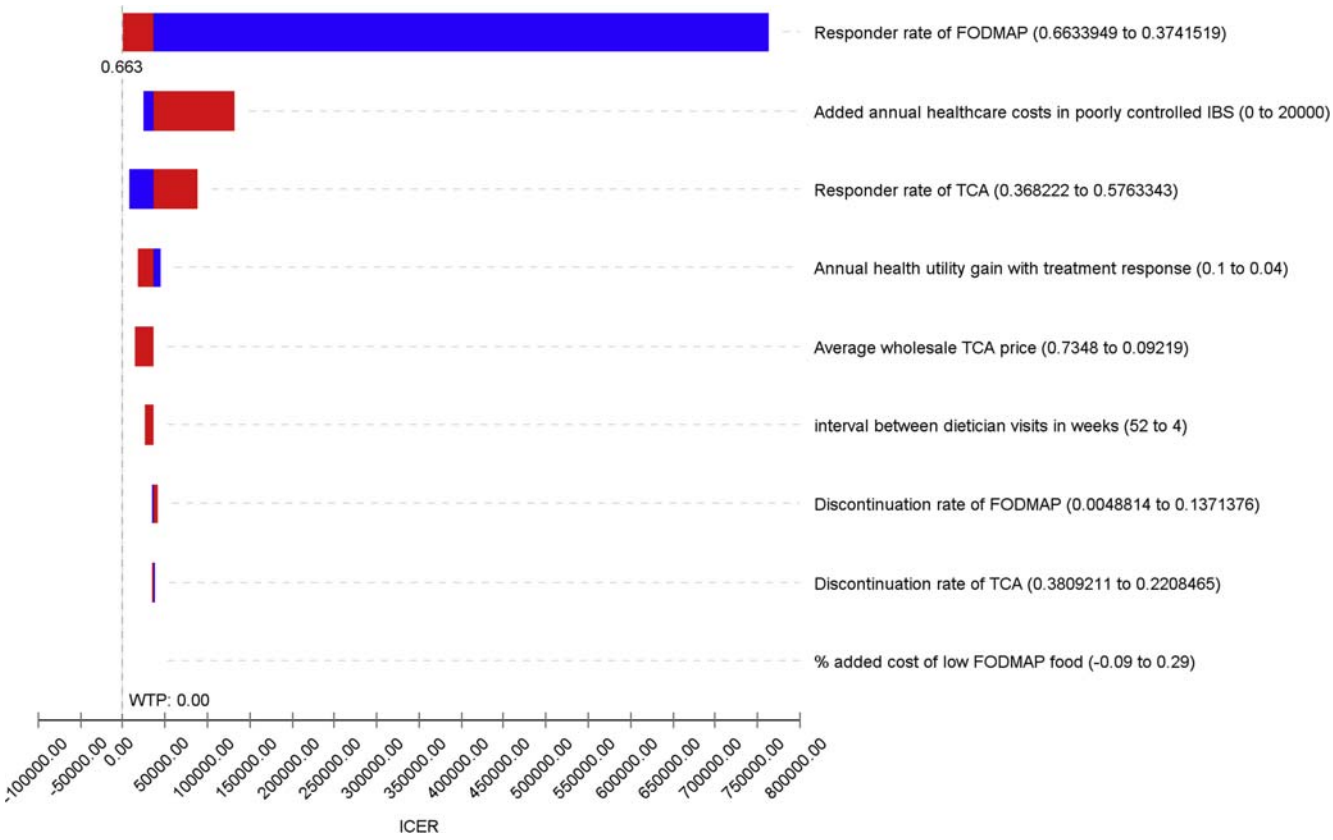
Supplementary Figure 13. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of eluxadoline compared with TCA from an insurer perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for eluxadoline referenced against TCA, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. TCA remains more effective and less expensive across the range of model inputs.



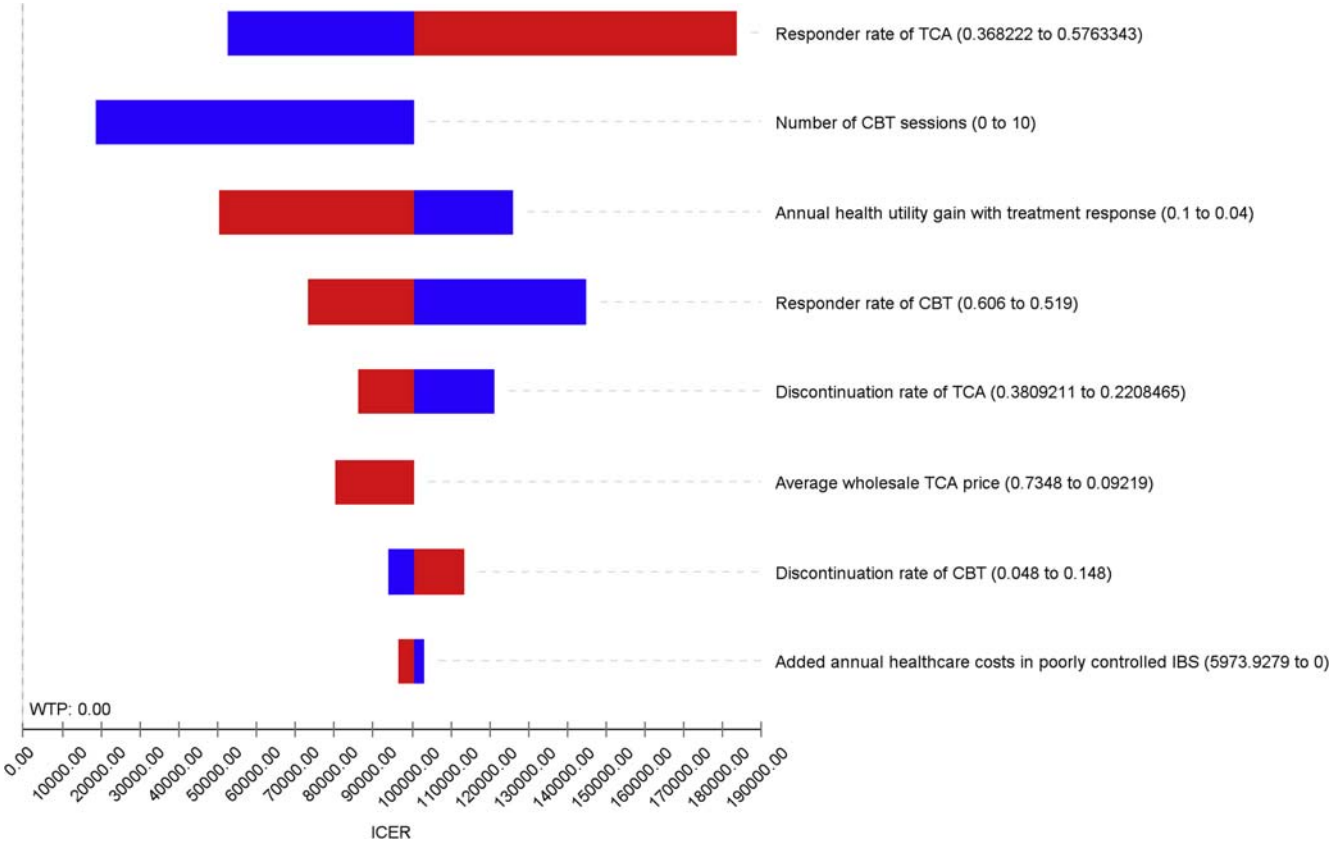
Supplementary Figure 14. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of eluxadoline compared with low FODMAP from an insurer perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for eluxadoline referenced against low FODMAP, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. Low FODMAP remains more effective and less expensive across the range of model inputs.



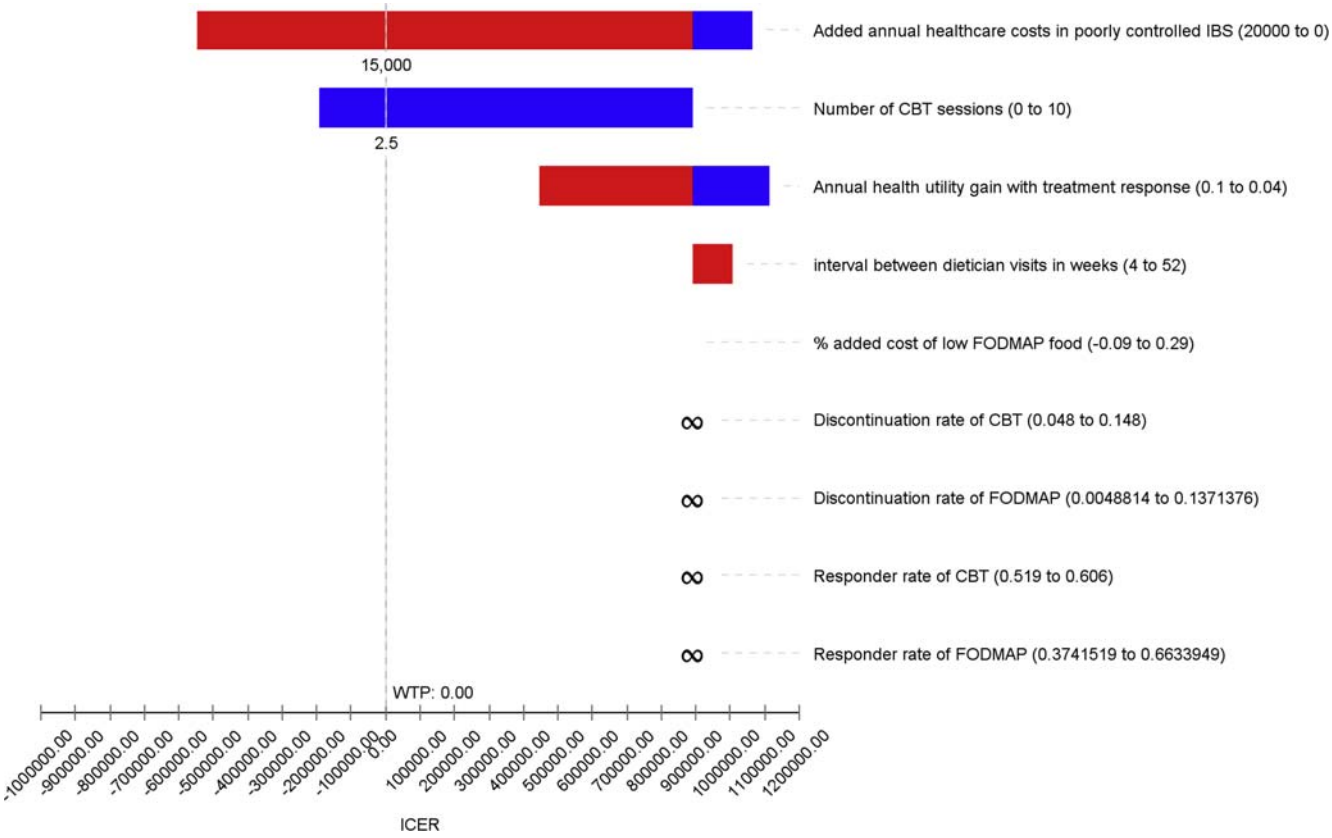
Supplementary Figure 15. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of eluxadoline compared with CBT from an insurer perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for eluxadoline referenced against CBT, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. CBT remains more effective and less expensive across the range of model inputs, unless the average wholesale price of eluxadoline was below $5.26 per pill.



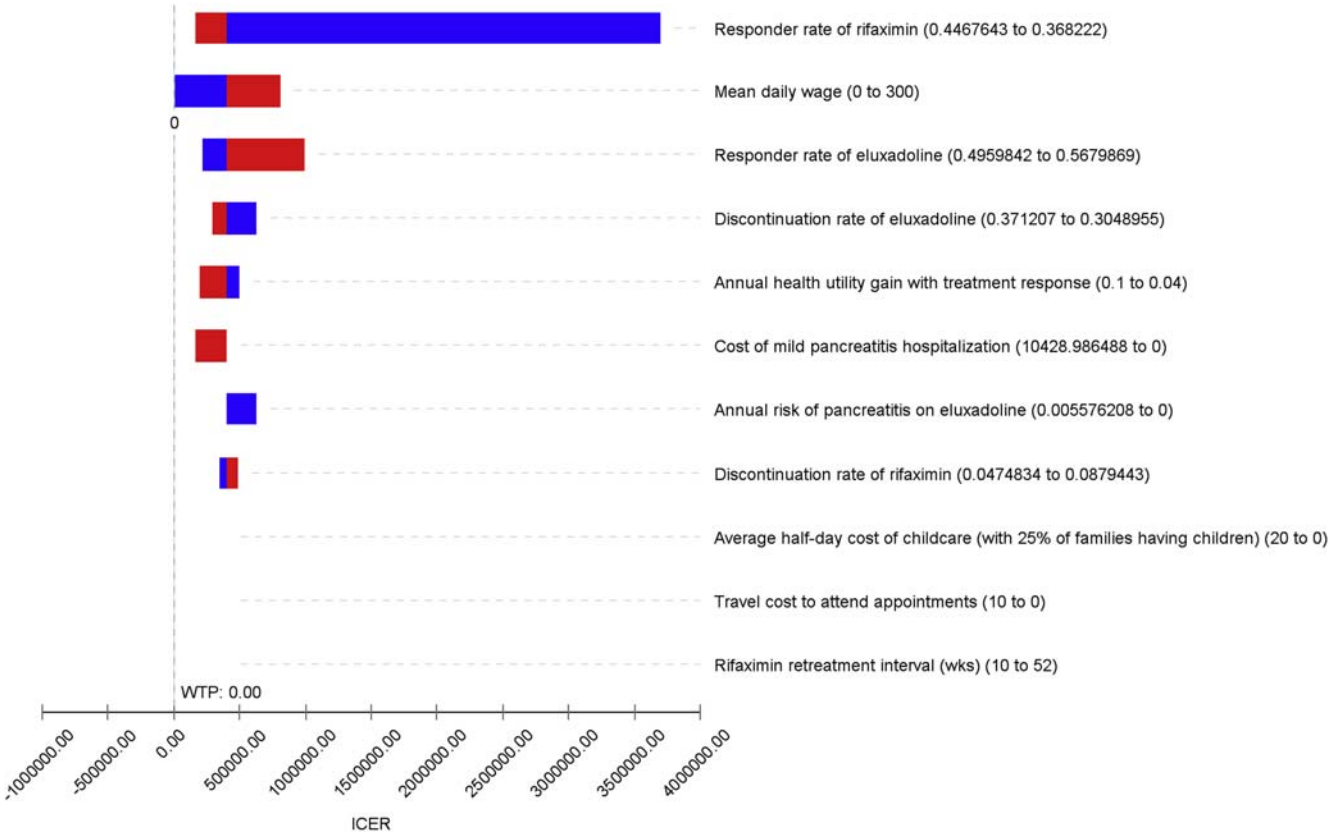
Supplementary Figure 16. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of low FODMAP compared with TCA from an insurer perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for low FODMAP referenced against TCA, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. Preference toward low FODMAP or TCA is highly dependent on the willingness to pay threshold across the range of model inputs.



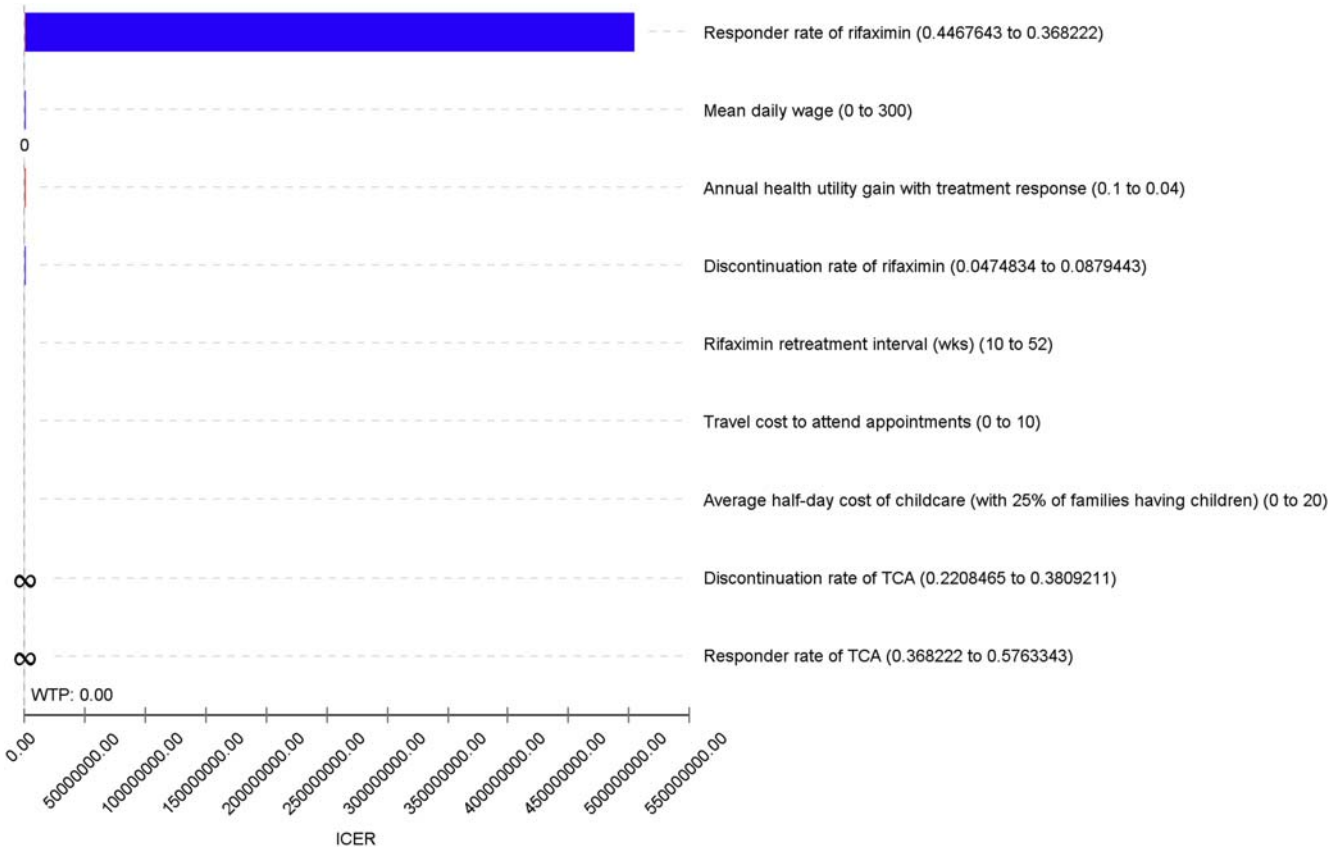
Supplementary Figure 17. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of CBT compared with TCA from an insurer perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for CBT referenced against TCA, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. Preference toward low FODMAP or TCA is highly dependent on the willingness to pay threshold across the range of model inputs.



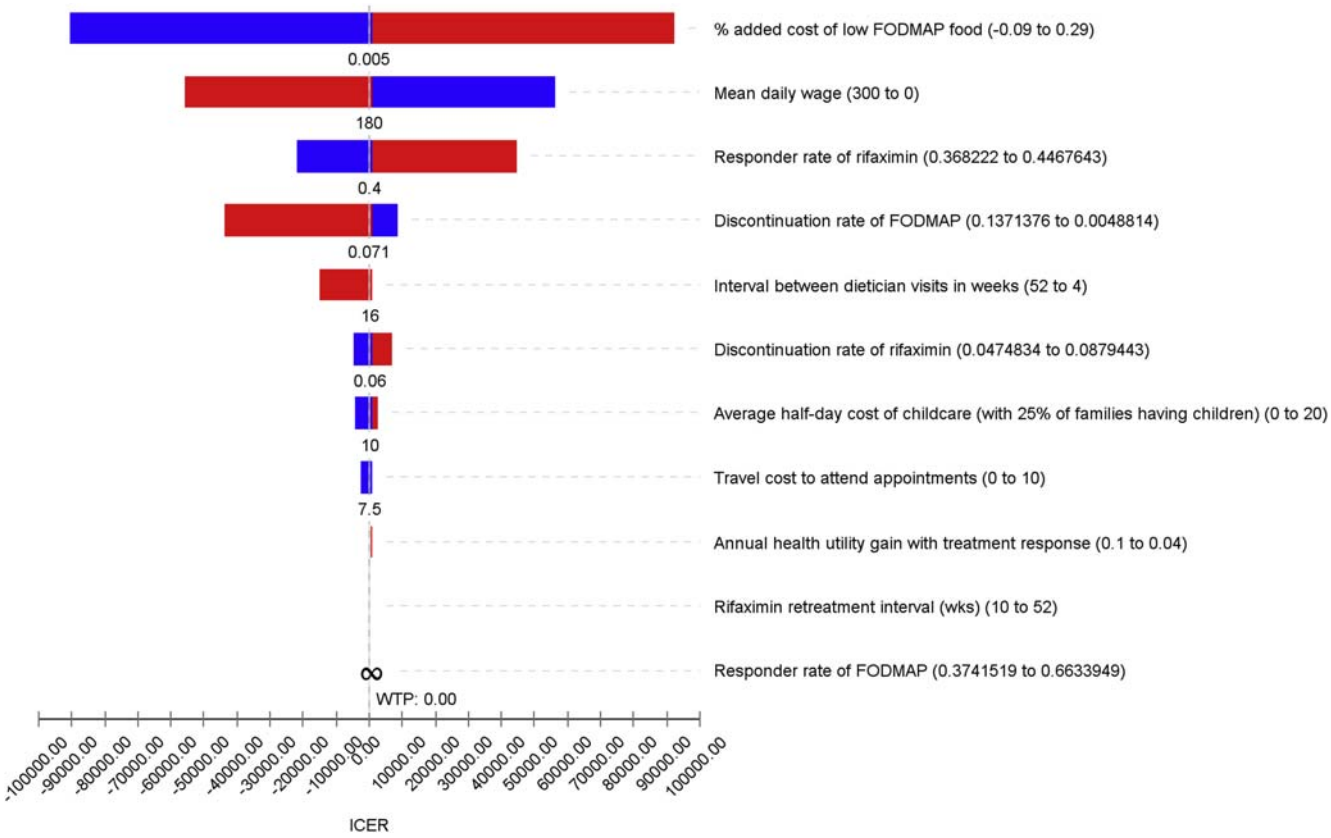
Supplementary Figure 18. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of CBT compared with low FODMAP from an insurer perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for CBT referenced against low FODMAP, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. CBT is more expensive but more effective than low FODMAP for all model inputs, but CBT can be less expensive than low FODMAP by reducing the visits needed in the CBT protocol or in patients with high annual health care costs because of uncontrolled IBS.



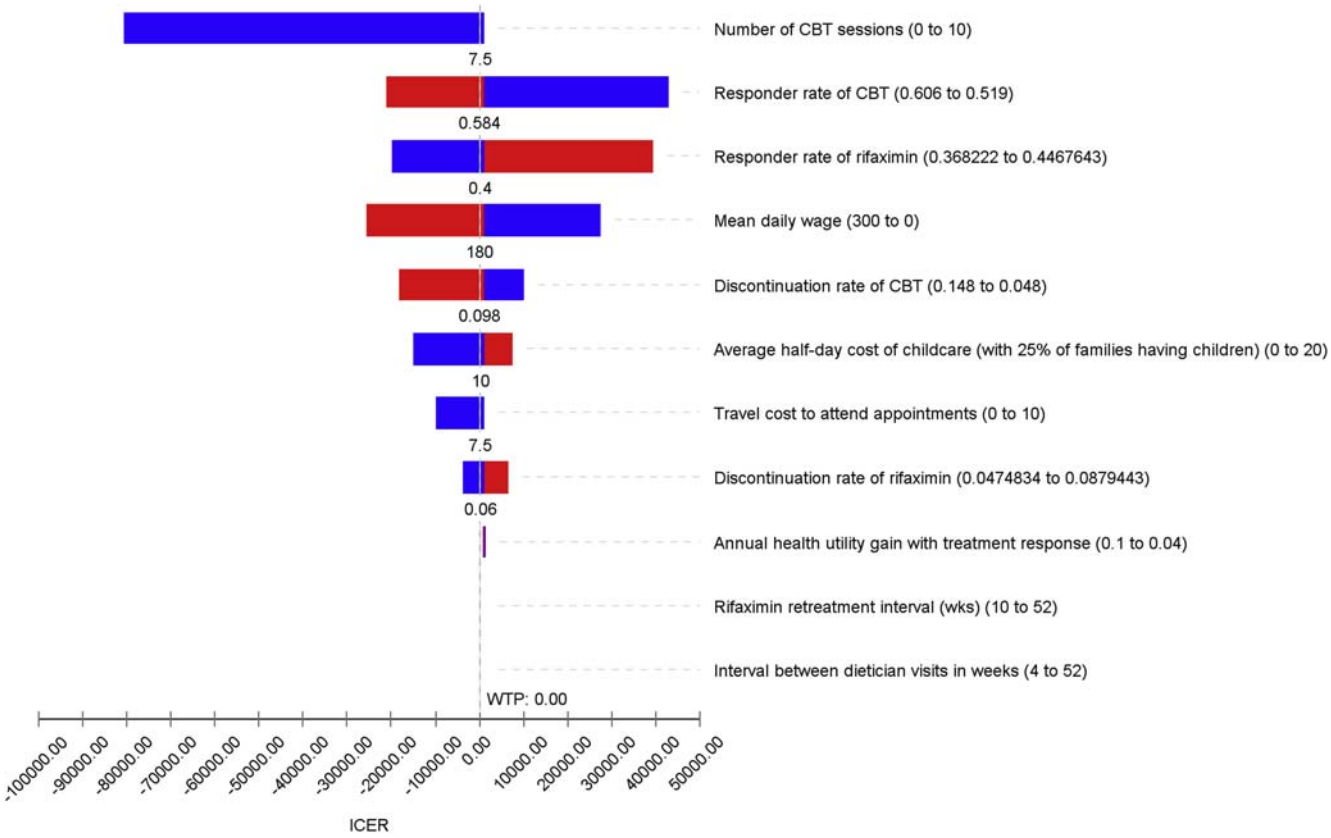
Supplementary Figure 19. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of rifaximin compared with eluxadoline from a patient perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for rifaximin referenced against eluxadoline, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. Rifaximin was preferred unless the mean daily wage approached $0.



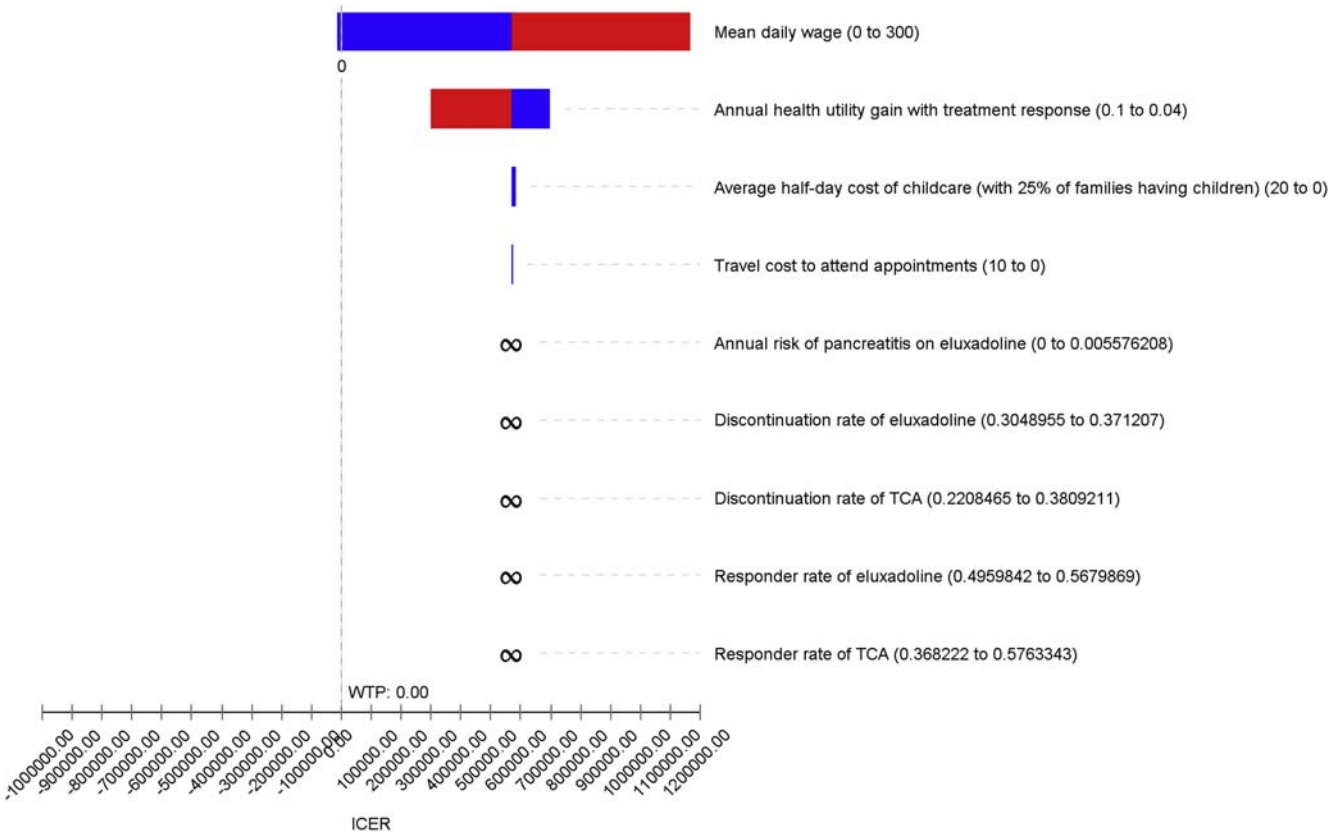
Supplementary Figure 20. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of rifaximin compared with TCA from a patient perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for rifaximin referenced against TCA, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. Rifaximin remains more effective but more expensive across the range of model inputs, with the exception of mean wages. From a patient perspective, the cost of rifaximin and TCA are similar as wages approach $0.



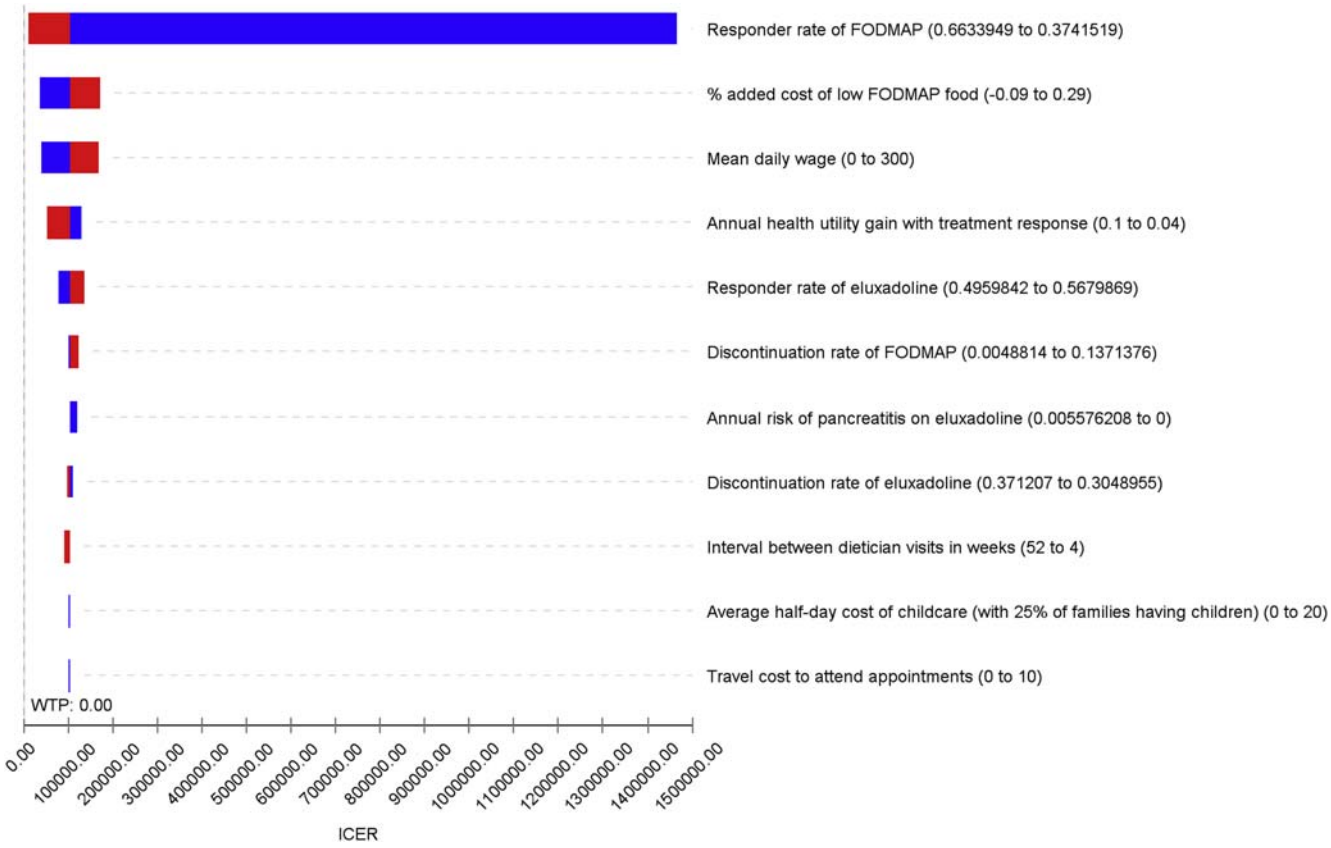
Supplementary Figure 21. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of low FODMAP compared with rifaximin from a patient perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for low FODMAP referenced against rifaximin, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. Several model inputs can significantly influence relative cost of treatment depending on the willingness-to-pay threshold.



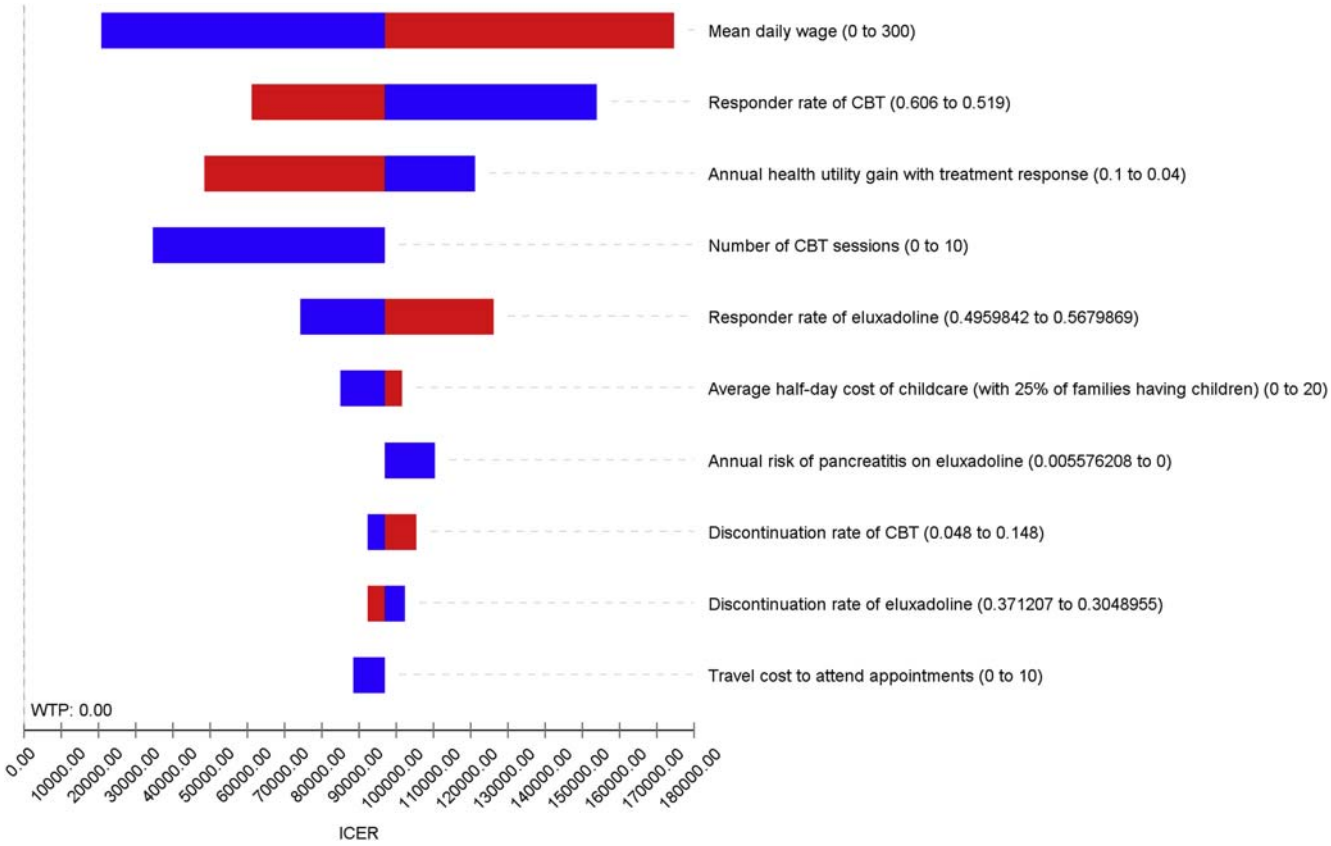
Supplementary Figure 22. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of CBT compared with rifaximin from a patient perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for CBT referenced against rifaximin, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. CBT is more effective but more expensive than rifaximin in base-case analysis; however, several model inputs can significantly influence relative cost of treatment. Several model inputs can significantly influence relative cost of treatment depending on the willingness-to-pay threshold.



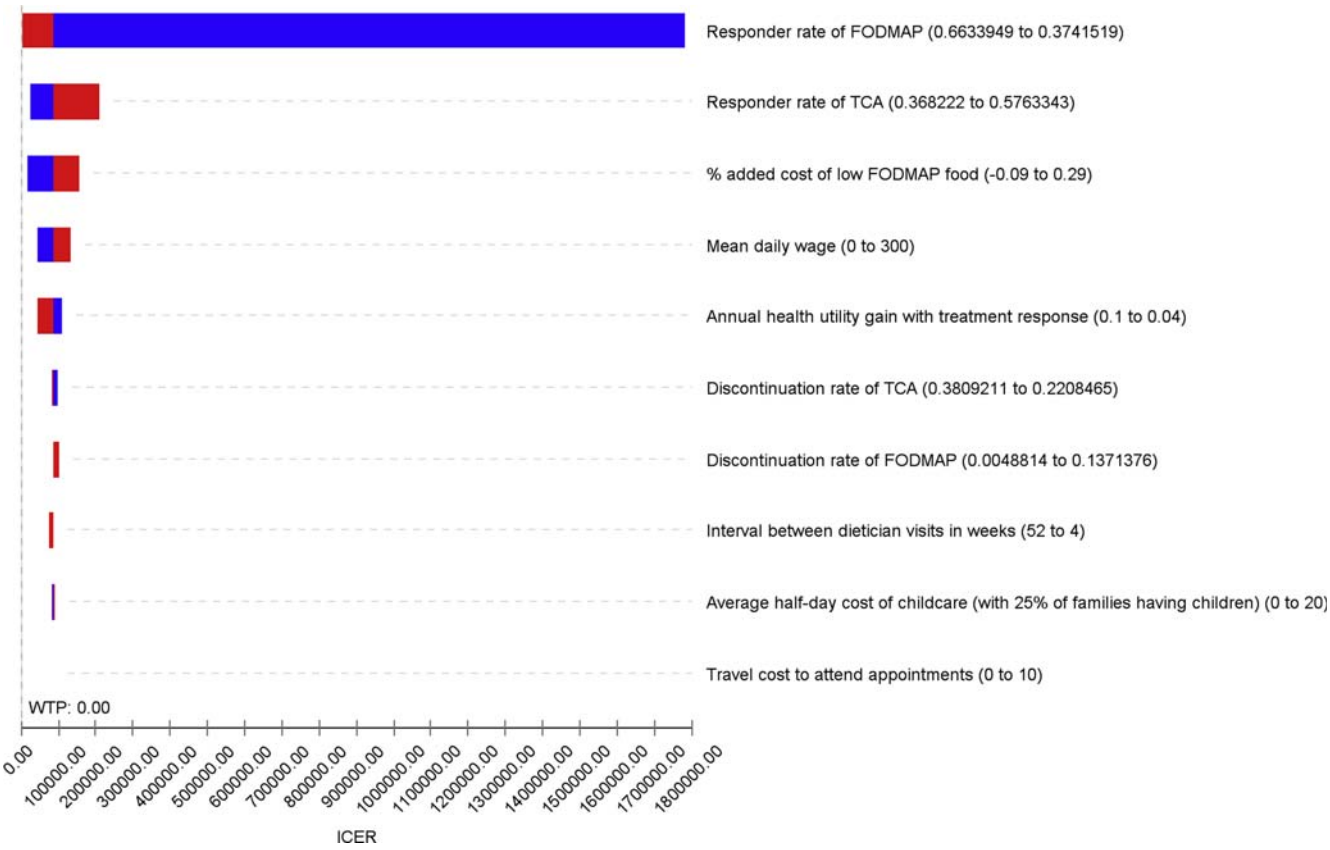
Supplementary Figure 23. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of TCA compared with eluxadoline from a patient perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for TCA referenced against eluxadoline, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. TCA remains more effective but more expensive across the range of most model inputs; however, TCA can become less expensive than eluxadoline among individuals with fewer work-days lost to IBS and individuals with lower wages.



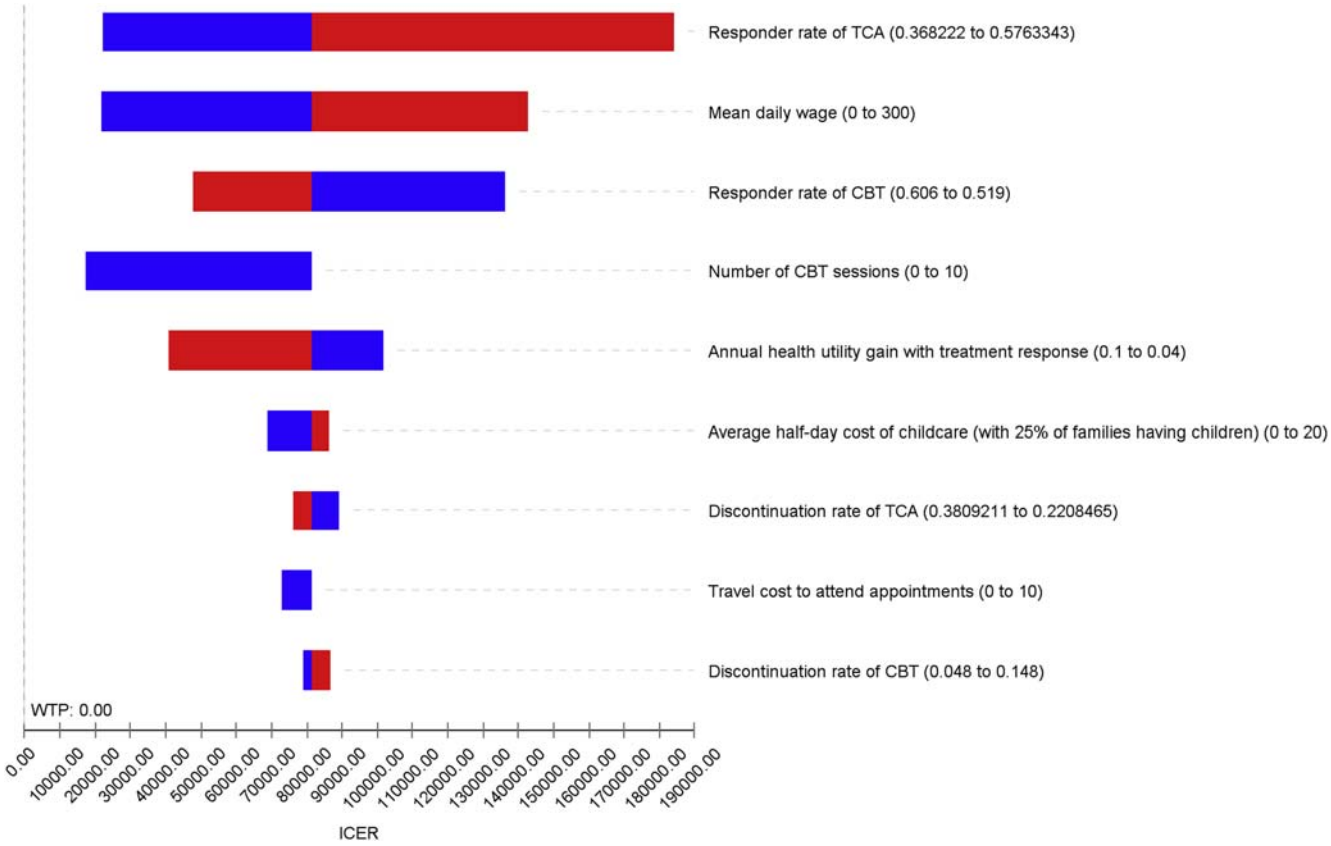
Supplementary Figure 24. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of low FODMAP compared with eluxadoline from a patient perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for low FODMAP referenced against eluxadoline, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. Several model inputs can significantly influence relative cost of treatment depending on the willingness-to-pay threshold.



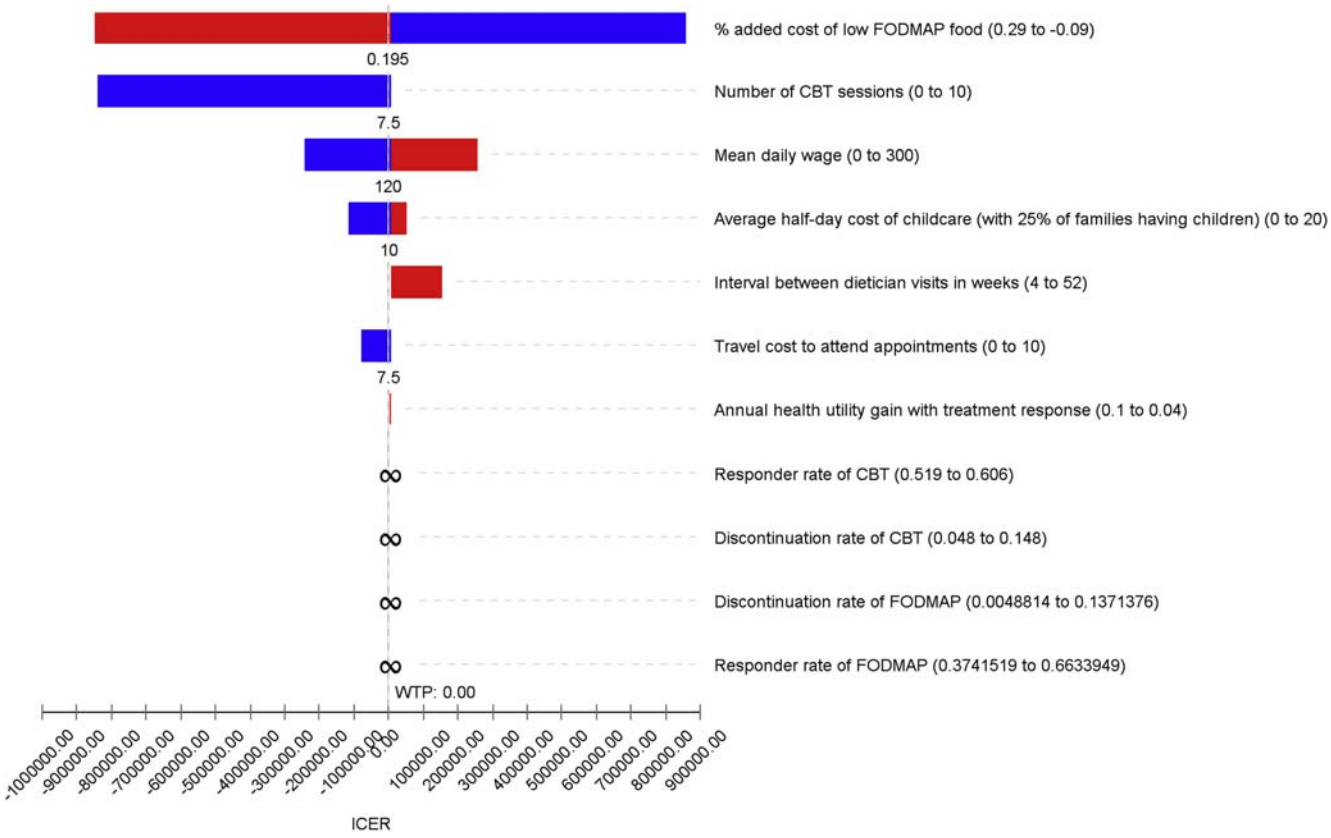
Supplementary Figure 25. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of CBT compared with eluxadoline from a patient perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for CBT referenced against eluxadoline, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. Several model inputs can significantly influence relative cost of treatment depending on the willingness-to-pay threshold.



Supplementary Figure 26. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of low FODMAP compared with TCA from a patient perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for low FODMAP referenced against TCA, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. Several model inputs can significantly influence relative cost of treatment depending on the willingness-to-pay threshold.



Supplementary Figure 27. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of CBT compared with TCA from a patient perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for CBT referenced against TCA, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. Several model inputs can significantly influence relative cost of treatment depending on the willingness-to-pay threshold.



Supplementary Figure 28. Multiple 1-way sensitivity analyses to assess the influence of the range of model inputs on cost-effectiveness of CBT compared with low FODMAP from a patient perspective. Results are presented as a tornado diagram. ICER is presented on the x-axis for CBT referenced against low FODMAP, with each *horizontal bar* representing how ICER changes throughout the expected range for each model input. CBT is slightly more effective and more expensive than low FODMAP in base-case analysis. CBT can be less expensive than low FODMAP among individuals with lower childcare costs, lower transportation costs, fewer required CBT sessions, or higher expected low FODMAP food costs. CBT can also be less expensive among individuals with more work-days lost to untreated IBS or lower wages. Wages and work-days lost have opposite effects, because individuals with higher wages would favor low FODMAP due to the time away from work required to complete CBT.

Supplementary Table 1. Design of Treatment Strategies for IBS-D

Treatment	Design
Peppermint oil[a]	90 mg twice daily
Probiotic[a]	Once daily
Anticholinergic antispasmodics[b]	Dicyclomine 10 mg 4 times daily
Loperamide	2 mg twice daily
Eluxadoline	100 mg twice daily
Rifaximin[c]	550 mg 3 times daily for 2 wk with retreatment every 4 mo
Tricyclic antidepressant[d]	Pretreatment ECG obtained in all patients Efficacy and tolerability (desipramine): 50 mg once daily for 1 wk, then 100 mg once daily for 1 wk, then 150 mg daily Cost (amitriptyline): 25 mg once daily
Cognitive behavioral therapy	One 60-min visit including intake followed by 9 visits of 45 min
Low FODMAP diet	Initial 60-min dietitian visit then 1 follow-up visit at 6 wk[2]

NOTE. The design of each drug treatment regimen (dosing and frequency for drug or supplement interventions; number and timing of visits for dietary and psychological interventions) was based on Food and Drug Administration labeling for drug therapies when available, otherwise the design was based on methodology reported in relevant clinical trials identified in prior systematic reviews.
ECG, electrocardiogram; IBS-D, irritable bowel syndrome with diarrhea.
[a]Efficacy and tolerability data for peppermint and probiotic supplements were derived, respectively, from IBGard (IM HealthScience LLC, Boca Raton, FL) and Align (Proctor and Gamble, Cincinnati, OH) trials, which represent the lowest-priced products within each class of intervention at the time of our search on January 30, 2019 among individual products listed in prior systematic review.[3]
[b]Efficacy and tolerability data for anticholinergic antispasmodics were derived from dicyclomine trials, which represents the lowest-priced drug within this drug class at the time of our search on January 30, 2019 among individual products listed in prior systematic review.[4]
[c]The assumed rifaximin retreatment interval of 17.3 weeks was based on published clinical experience and methodology in the TARGET 3 (phase III) US randomized clinical trial.
[d]Efficacy and tolerability were derived from multicenter randomized controlled trial data evaluating desipramine. Cost data were derived from amitriptyline data, which represented the lowest-priced drug within the TCA drug class[5] at the time of our search on August 26, 2020. In contrast, the cost of desipramine was $0.73/pill. We assumed similar efficacy and tolerability for amitriptyline and desipramine in managing IBS-D.

Supplementary Table 2. Model Inputs

Description	Base-case value	Distribution	References
Outcomes			
Eluxadoline responder rate	53.2%	Beta; n = 763	Black et al,[6] FDA Medical Review, Table 29 2015[7]
Eluxadoline discontinuation rate	33.7%	Beta; n = 809	Black et al,[6] Lembo et al, 2016[8]
Risk of acute pancreatitis with eluxadoline use	0.006%	Range, 0.0% to 0.006% in sensitivity analysis	FDA Medical Review 2015[7]
Duration of acute pancreatitis associated with eluxadoline use	2 d	Range, 1 to 30 d in sensitivity analysis	Cash et al, 2017[9]
Rifaximin responder rate	40.7%	Beta; n = 624	Black et al,[6] Pimentel et al, 2011[10]
Rifaximin discontinuation rate	6.6%	Beta; n = 625	Black et al,[6] Pimentel et al, 2011[10]
Rifaximin retreatment interval	17.3 wk	Range, 10 to 52 wk in sensitivity analysis	Lembo et al, 2016[11] Pimentel et al, 2011[12]
TCA responder rate	48.9%	Beta; n = 135	Drossman et al, 2003[13] Ford et al, 2019[5]
TCA discontinuation rate	29.6%	Beta; n = 135	Drossman et al, 2003[13] Ford et al, 2019[5]
Low FODMAP discontinuation rate	4.0%	Beta; n = 50	Dionne et al, 2018[14] Eswaran et al, 2016[2]
Interval between initial and follow-up dietitian visits	6 wk	Range, 6 to 52 wk in sensitivity analysis	Dionne et al, 2018[14] Eswaran et al, 2016[2]
Length of follow-up dietitian visits	30 min		Dionne et al, 2018[14] Eswaran et al, 2016[2]
Number of CBT visits	10	Range, 6 to 12 visits in sensitivity analysis	Ford et al, 2019[5] Lackner et al, 2018[15]
CBT responder rate	56.3%	Beta; n = 495	Ford et al, 2019[5]
CBT discontinuation rate	9.0%	Beta; n = 146	Lackner et al, 2018[15]
Anticholinergic antispasmodic responder rate	56.3%	Beta; n = 48	Page and Dirnberger, 1981[16] Ruepert et al, 2011[4] Ford et al, 2008[17]

Supplementary Table 2. Continued

Description	Base-case value	Distribution	References
Anticholinergic antispasmodic discontinuation rate	14.6%	Beta; n = 146	Page and Dirnberger, 1981[16] Ruepert et al, 2011[4] Ford et al, 2008[17]
Loperamide responder rate	60.0%	Beta; n = 10	Hovdenak, 1987[18]
Loperamide discontinuation rate	4.7%	Beta; n = 43	Hovdenak, 1987[18] Lavö et al, 1987[19]
Peppermint oil supplement responder rate	75.4%	Beta; n = 124	Ruepert et al, 2011[4]
Peppermint oil supplement discontinuation rate	5.1%	Beta; n = 197	Ruepert et al, 2011[4]
Probiotic supplement responder rate	48.8%	Beta; n = 330	Ford et al, 2014[3]
Probiotic supplement discontinuation rate	6.4%	Beta; n = 330	Ford et al, 2014[3]
Work-days lost per year	6.0	Triangular (range, 2.4 to 88.4 d/y)	Drossman et al, 1993[20] Hahn et al, 1999[21] Hungin et al, 2003[22] Hungin et al, 2005[23] Buono et al, 2017[24]
QALYs			
Health utility associated with therapeutic response	0.78	Range, 0.77 to 0.83 in sensitivity analysis	Spiegel et al, 2009[25]
Health utility associated with therapeutic nonresponse	0.73		Spiegel et al, 2009[25]
Costs			
Cost of eluxadoline 100-mg pill	$21.03	Range, $0 to $20.15 in sensitivity analysis	Medicaid NADAC Database[26]
Cost of rifaximin 550-mg pill	$40.88	Range, $0 to $37.92 in sensitivity analysis	Medicaid NADAC Database[26]
Cost of TCA (base-case = amitriptyline 25-mg pill)	$0.14	Range, $0 to $0.73 in sensitivity analysis (highest cost = desipramine 25-mg pill)	Medicaid NADAC Database[26]
Cost of office-based electrocardiogram	$33.00		Healthcare Bluebook[27]
Cost of loperamide 2-mg pill	$0.23		Medicaid NADAC Database[26]
Initial CBT visit (CPT 96156)	$99.97		CMS Physician Fee Schedule[28]

Supplementary Table 2. Continued

Description	Base-case value	Distribution	References
Follow-up CBT visit (CPT 96158+96159*2)	$115.85		CMS Physician Fee Schedule[28]
Initial dietitian visit (CPT 97802 x4)	$153.00		CMS Physician Fee Schedule[28]
Follow-up dietitian visit (CPT 97803 x2)	$66.40		CMS Physician Fee Schedule[28]
Cost of usual US diet per day	$21.08		US Bureau of Labor Statistics[29]
Change in food costs of low FODMAP vs usual diet	+10.0%	Range, -9.0% to +29.0% in sensitivity analysis	Gearry et al, 2009[30]
Cost of peppermint oil tablet supplement	$0.54		Amazon.com[31]
Cost of probiotic tablet supplement	$0.77		Amazon.com[32]
Cost of dicyclomine 10-mg capsule	$0.29		Medicaid NADAC Database[26]
Average daily 2019 fourth-quarter US wage for full-time employment	$148.50	Range, $0 to $300.00 in sensitivity analysis	US Bureau of Labor Statistics[33]
Cost of admission for mild pancreatitis	$11,462.34		HCUPnet[34]
Cost of office visit for IBS-D (CPT 99214)	$110.28		CMS Physician Fee Schedule[28]
Half-day cost of childcare to attend clinic (accounting for 25% of US households having children)	$58.00	Range, $0 to $80.00 in sensitivity analysis	US Census Bureau[35] Cost of Care Survey[36]
Transportation to/from medical visits	$10.00	Range, $0 to $10.00 in sensitivity analysis	Muennig, 2008[37]
Annual added health care cost of untreated IBS-D	$2141.05	Range, $0 to $10,000/y in sensitivity analysis	Buono et al, 2017[38]

NOTE. All costs are up to date as of August 26, 2020 and are discounted forward at a 3% rate as appropriate.
CBT, cognitive behavioral therapy; CMS, Center for Medicare and Medicaid Services; CPT, Computerized Procedure Terminology; FDA, Food and Drug Administration; IBS-D, irritable bowel syndrome with diarrhea; NADAC, National Average Drug Acquisition Cost; QALY, quality-adjusted life year; TCA, tricyclic agent.

Supplementary Table 3. Comparative Cost-effectiveness of Low FODMAP Diet, CBT, and Drug/Supplement Interventions Supported by Low/Very Low Quality of Evidence

Strategy	Total cost ($/y)	Total effectiveness (QALY-gained)	Incremental cost ($)	Incremental effectiveness (QALY)	ICER ($/QALY-gain)
Societal perspective					
Peppermint oil	$2074.66	0.036	—	—	Reference
No treatment	$6930.17	0.730	—	—	Dominated by peppermint oil
Probiotics	$3689.50	0.753	—	—	Dominated by peppermint oil
Anticholinergic antispasmodics	$2988.46	0.024	—	—	Dominated by peppermint oil
Low FODMAP	$3953.32	0.025	—	—	Dominated by peppermint oil
CBT	$4469.35	0.026	—	—	Dominated by peppermint oil
Loperamide	$2316.58	0.015	—	—	Dominated by peppermint oil
Insurer perspective					
Peppermint oil	$524.26	0.036	—	—	Reference
No treatment	$2141.05	0.730	—	—	Dominated by peppermint oil
Probiotics	$1058.14	0.753	—	—	Dominated by peppermint oil
Anticholinergic antispasmodics	$1037.60	0.024	—	—	Dominated by peppermint oil
Low FODMAP	$1242.62	0.025	—	—	Dominated by peppermint oil
CBT	$1808.95	0.026	—	—	Dominated by peppermint oil
Loperamide	$1637.12	0.015	—	—	Dominated by peppermint oil
Patient perspective					
Peppermint oil	$1550.40	0.766	—	—	Reference
No treatment	$4789.13	0.730	—	—	Dominated by peppermint oil
Probiotics	$2631.36	0.753	—	—	Dominated by peppermint oil
Anticholinergic antispasmodics	$1950.86	0.754	—	—	Dominated by peppermint oil
Low FODMAP	$2730.29	0.755	—	—	Dominated by peppermint oil
CBT	$2734.14	0.756	—	—	Dominated by peppermint oil
Loperamide	$1637.12	0.745	—	—	Dominated by peppermint oil

NOTE. QALYs-gained per year are rounded to the nearest thousandth in this table. Costs and ICERs are rounded to the nearest $0.01 in this table. ICER are rounded based on actual underlying values.
CBT, cognitive behavioral therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.