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Economic Evaluation

Cost-Effectiveness of an Extended-Role General Practitioner Clinic for Persistent Physical Symptoms: Results From the Multiple Symptoms Study 3 Pragmatic Randomized Controlled Trial

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ABSTRACT

Objectives: This study aimed to evaluate the cost-effectiveness of an extended-role general practitioner symptoms clinic (SC), added to usual care (UC) for patients with multiple persistent physical symptoms (sometimes known as medically unexplained symptoms).

Methods: This was a 52-week within-trial cost-utility analysis of a pragmatic multicenter randomized controlled trial comparing SC + UC (n = 178) with UC alone (n = 176), conducted from the primary perspective of the UK National Health Service and personal and social services (PSS). Base-case quality-adjusted life-years (QALYs) were measured using EQ-5D-5L. Missing data were imputed using multiple imputation. Cost-effectiveness results were presented as incremental cost-effectiveness ratios and incremental net monetary benefits. Uncertainty was explored using cost-effectiveness acceptability curves (using 1000 nonparametric bootstrapped samples) and sensitivity analysis (including societal costs, using SF-6D and ICECAP-A capability measure for adults outcomes to estimate QALYs and years of full capability, respectively, varying intervention costs, missing data mechanism assumptions).

Results: Multiple imputation analysis showed that compared with UC alone, SC + UC was more expensive (adjusted mean cost difference: 704; 95% CI £605-£807) and more effective (adjusted mean QALY difference: 0.0447; 95% CI 0.0067-0.0826), yielding an incremental cost-effectiveness ratio of £15 765/QALY, incremental net monetary benefit of £189.22 (95% CI −£573.62 to £948.28) and a 69% probability of the SC + UC intervention arm being cost-effective at a threshold of £20 000 per QALY. Results were robust to most sensitivity analyses but sensitive to missing data assumptions (2 of the 8 scenarios investigated), SF-6D, and ICECAP_A capability measure for adults quality-of-life outcomes.

Conclusions: A symptoms clinic is likely to be a potentially cost-effective treatment for patients with persistent physical symptoms.

Keywords: cost-effectiveness analysis, cost-utility analysis, extended-role GP, persistent physical symptoms, symptom clinic.

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Highlights

- Persistent physical symptoms is a common problem, affecting patients' quality of life with substantial costs to health services and society.
- To our knowledge, this is the first economic evaluation to assess the value added by an extended-role general practitioner symptoms clinic compared with usual care (UC) in primary care.
- Symptoms clinic + UC has the potential to be cost-effective compared with UC alone in a 12-month time horizon, yielding increased quality-adjusted life-years at reasonable cost using a threshold £20 000 per quality-adjusted life-year gained.

Introduction

Persistent physical symptoms that are disproportionate to detectable physical disease are common in all clinical settings. They are present in up to 40% of primary care consultations[1] and account for a similar proportion of referrals from general practitioners to specialists.[2] Approximately 2% of adults experience multiple physical symptoms at a level that has a significant impact on their quality of life.[3,4] These symptoms may occur in clusters, as in syndromes such as irritable bowel syndrome or fibromyalgia, or be classified broadly as functional disorders.[5] Persistent physical symptoms account for substantial costs to health services and society.[6-8]

Historically, persistent physical symptoms have been referred to as medically unexplained symptoms and before that as somatization, implying that they represent mental distress and not bodily change. Current formulations of persistent symptoms involve complex interactions of body and brain systems,[9,10] including the ways in which bodily sensations are experienced and interpreted in the light of past and current experiences.[11] For these reasons, and because of patient preference,[12] we prefer the term persistent physical symptoms. However, we recognize that many health professionals and some research groups continue to use the term medically unexplained symptoms, and in comparing studies, we will regard the terms as interchangeable.

Both pharmacological[13] and nonpharmacological treatments[14] have been evaluated. There are no guideline-recommended medications in the United Kingdom for persistent physical symptoms. Psychological therapies, such as cognitive behavioral

therapy, have small effects across a range of symptoms,[14] and other psychological therapies have similar effects.[15,16] These have generally been tested in secondary care settings. Despite the prevalence of persistent physical symptoms in primary care, 2 recent reviews concluded that there are no effective primary care–based treatments.[17,18] Potential outcomes for measuring the effectiveness of interventions include self-report measures of symptoms such as the PHQ-15,[19] quality-of-life measures with validity in this field, such as the EQ-5D,[20] and healthcare use.[21]

We developed an extended consultation intervention for people with persistent physical symptoms using extended-role general practitioners (erGPs) to deliver a symptoms clinic (SC).[22,23] The aim of the intervention is to recognize and validate the experience of the patient, work with them to reach an explanation for their persistent physical symptoms that makes sense,[24-26] and use this to agree upon actions to manage symptoms or limit their impact.[27] We evaluated the effectiveness of the SC in a randomized controlled trial (Multiple Symptoms Study 3 [MSS3]) with an economic evaluation conducted alongside, to assess the cost-effectiveness of a SC + usual care (UC) versus UC alone.[28] To our knowledge, this study seems to be the first assessing the value for money generated by a primary care–based SC intervention, delivered by erGPs, thus generating increased understanding on the potential costs and broader health and well-being outcomes generated by such an intervention.

Methods

Study Design

A within-trial economic evaluation was conducted alongside the MSS3 trial. MSS3 was a pragmatic, multicenter, individually randomized parallel-group controlled trial investigating the clinical effectiveness of the addition of SC to UC versus UC alone, to improve the primary outcome of physical symptoms, which was measured using PHQ-15[19] at 52 weeks after randomization, for patients with the common problem of persistent (medically unexplained) physical symptoms.

Full details of the randomized controlled trial protocol, on the study design, participating centers, and participants are reported elsewhere,[28] and the results of the evaluation of the clinical effectiveness have recently been published.[29] The flow of participants through the trial is summarized as a flowchart (Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.09.015), but briefly, the study involved 354 adult participants recruited from GP practices in 4 regions/centers of England in the United Kingdom. Participants were potentially eligible if they had at least one symptom syndrome code within GP electronic records, 2 or more specialist referrals in the preceding 3 years, and multiple physical symptoms (PHQ-15 between 10 and 20). They were excluded, however, if they had diseases likely to cause multiple symptoms or disability. Detailed code lists are in the published protocol.[28] We have added "symptom syndrome codes such as those for irritable bowel syndrome or fibromyalgia." We have also clarified if they had diseases likely to cause multiple symptoms or disability, either coded in the GP electronic health record or in their GP's opinion. The trial involved people with lived experience of multiple physical symptoms in its design and included a patient and public coinvestigator.[28]

Study participants were randomly assigned to 1 of 2 arms:

SC intervention plus UC group (SC + UC): UC enhanced by a SC intervention.

UC-alone control group: participants continued to receive UC from their usual general practice, that is, UC comprised consultation as needed with the primary care team with no restriction on prescribing, diagnostic testing, or referral.

The SC intervention is a sequence of medical consultations, which aim to elicit a detailed clinical history, ensure that the patient's experience is fully heard and validated, to offer rational explanations for symptoms, and to assist the patient to develop ways of managing their symptoms. It harnesses GPs' skills as clinical generalists across biomedical and psychosocial domains and as interpretive practitioners.[30] The treatment model can be summarized under 4 headings: recognition, explanation, action, and learning; content, teaching, and delivery of this are described elsewhere.[27] The SC consists of up to 4 consultations with an erGP over 6 to 12 weeks. These comprise an initial long consultation (approximately 50 minutes) followed by up to 3 medium-length consultations (15-20 minutes); erGPs had flexibility to increase the gaps between sessions if required. Clinic attenders received a SMS reminder the day before each SC appointment and were offered a further appointment if they missed an appointment. Consultations before March 2020 were delivered face to face. Subsequently, consultations took place via video consultation or telephone.

The clinic was delivered by 6 erGPs working outside their usual practices, initially face to face and subsequently via video consultation in response to the COVID-19 pandemic. Each erGP received 13 half-day sessions of training (over 6.5 days total) before the trial, including 5 days (10 sessions, which included initial training, sessions for personal review, assessment and feedback, and doing practice clinics), then follow-up meetings and then regular ongoing supervision. Participants' completed assessments at baseline, 13, 26, and 52 weeks after randomization. The within-trial analysis economic evaluation framework was a cost-utility analysis, conducted from the perspective of the UK National Health Service (NHS) and Personal Social Services (PSS) as per National Institute for Health and Care Excellence (NICE) guidance[31] in the primary base-case analysis.

Resource Use and Costs

Individual-level healthcare resource use data were collected using self-reported questionnaires at 26 and 52 weeks. Resource use included visits and/or telephone contacts and treatments to NHS primary care (eg, GP, practice nurse, and community physiotherapist), secondary care (eg, hospital outpatient visits, inpatient stay, and diagnostic tests), as well as patient costs (including private care visits and information on time of paid/unpaid work was captured to estimate productivity losses).

The unit costs used to value healthcare resource use and time losses are reported in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.09.015. Standard unit costs from published UK sources were used to value the NHS resources.[32-35] Private care was costed using estimates of tests and treatments based on information from the published literature and obtained from private providers.[36,37] All costs were reported in 2021/22 prices. Unit costs were adjusted for inflation where necessary using the NHS Cost Inflation Index.[32] Gross average wage rates (age/sex specific) obtained from the Annual Survey of Hours and Earnings, published by the Office for National Statistics, were used to value time lost from paid employment.[38] Time lost from unpaid work was costed using the published value of unpaid work by the Office for National Statistics, and the value of forgone education/training time was valued using the current value of nonworking time available from the Department of Transport.[39,40] The intervention cost was estimated by including the time spent on training sessions, delivering consultation sessions, and supervision. The number of sessions and their duration were based on

data collected during the trial. The unit costs used to value GP trainers' and erGPs' time and details of the basis for the intervention cost estimate are reported in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.09.015. UC costs are assumed common to both groups and not explicitly considered as part of the specific intervention delivery–related cost component itself.[41] However, costs included in the UC alone group are assumed to capture the resource use associated with routine UC costs.

Quality-of-Life Outcomes

Treatment effects were measured as QALYs (base-case analysis) and also years of full capability (YFC) (sensitivity analysis). For QALYs, the valuation of health states is based against death (a health state with an assumed value of 0); therefore, life years are adjusted for quality of years, with years of death having a quality adjustment value of 0. Thus, for QALYs, health state values are anchored on a perfect health to dead scale (1-0). For YFC, the anchors of the health state values are on a full capability-no capability scale (1-0). YFC (equivalent) represent the total amount of capability that is available over time; those who die have no capability and therefore would have 0 years of full capability from this point of death.

For the base-case analysis, utility scores were estimated using participant responses to the EQ-5D-5L[42] questionnaire at baseline and at each planned follow-up time point (13, 26, and 52 weeks). Additional analysis estimated utility scores using participant responses to the Short Form-12/SF-6D (SF-12)[43] and years of full capability using responses to the capability measure for adults (ICECAP-A)[44] questionnaires, respectively, at baseline and at each planned follow-up time point (26 and 52 weeks).

There are a number of important differences between these 3 QoL instruments. The EQ-5D-5L (asks participants to indicate "your health today") comprises 5 domains with 5 levels in each, including mobility, self-care, usual activities, pain and discomfort, and anxiety and depression; the SF-6D (asks participants to consider their health during the "past 4 weeks") comprises 6 dimensions with 4 to 6 levels in each, including physical function, role limitation, social functioning, pain, mental health, and vitality; the ICECAP (asks participants to consider their overall QoL "at the moment") has 5 attributes including attachment, stability, achievement, enjoyment, and autonomy. The EQ-5D index ranges between −0.594 (states worse than death) to 1.0 (full health). The SF-6D index usually ranges between 0 (states equal to death) and 1 (full health). The ICECAP-A is anchored on 1 (full capability) to 0 (no capability). The rationale for including all 3 measures, each with different descriptive systems, values applied to health states, and contextual basis, that is, recall period, aimed to provide a reliable and robust assessment of outcomes and the opportunity to compare the performance/responsiveness to change with the preferred measure (EQ-5D-5L), which is the focus of a separate related article.

Conversion of EQ-5D-5L responses to EQ-5D-3L values was based on the mapping function developed by the Decision Support Unit, using The Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions data set[45,46] as currently recommended by NICE.[31] Conversion of SF-12 responses to Short Form-6 Dimension (SF-6D) values was undertaken using a published UK tariff.[47] Conversion of ICECAP-A responses to YFC was undertaken using a published UK tariff/value set.[48] These utility/well-being scores were used to estimate QALYs (or YFC) over the 52-week period using the area under the curve method.

Cost-Utility Analysis

A health economics analysis plan was written and finalized before database lock and before beginning the analyses (available on request from the authors). The planned analysis evaluated costs and outcomes over a 12-month time horizon; therefore, discounting was not required. The planned primary economic analysis was performed on an intention-to-treat basis for participants with complete cost and EQ-5D data at each time point. However, only 166 (47%), 223 (63%), and 156 (44%) participants had complete cost, complete EQ-5D, and both complete cost/EQ-5D data, respectively. Therefore, the base-case analysis was informed by multiple imputation of missing data and covariate adjustment and a complete case analysis restricted to a sensitivity analysis because this could introduce bias, unless data were missing completely at random.[49] Details of the missing cost and health utility data, by treatment arm, statistical methods, including missing data imputation, rationale, and assumptions, are reported in Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.09.015. Additionally, the associations between missing costs and QALYs data and key baseline variables are reported in Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.09.015. Unadjusted descriptive analyses for clarity are reported as means with standard deviation or number in each group with between-group differences presented as raw, unadjusted differences. Differences between groups were compared using independent sample Student's t tests for QALYs and costs. Two-sided P values $<.05$ were regarded as significant.

To estimate adjusted differences in mean costs and QALYs between treatment groups, generalized linear models with adjustment for baseline age, sex, baseline PHQ-15, and baseline utility score[50] were performed. Using the modified Park test, Pearson's correlation, Pregniborn link and modified Hosmer-Lemeshow test, a Poisson family with power −0.65 link function and a Poisson family with 0.7 link function were specified for the cost and QALY data, respectively.[51] Recycled predictions were used to recover adjusted mean costs and QALYs by treatment allocation group and incremental differences between groups.[51] Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in total adjusted costs by the difference in adjusted QALYs. Regression outputs facilitated calculation of the incremental net monetary benefit (INMB) and associated CIs at the UK NICE's recommended willingness-to-pay threshold (WTP) range of between £20 000 and £30 000 per QALY. INMB is calculated as (incremental benefit × threshold) − incremental cost.

Assuming missingness at random, missing data were addressed using multiple imputation by chained equations[52,53] with predictive mean matching (kth-nearest neighbor = 5) to generate 60 imputed data sets (greater than the proportion of missing data[49] of 56% found in the MSS3 trial). The imputation model was adjusted for the same baseline characteristics as in the generalized linear models. Missing aggregated costs at the main cost categories level (NHS primary and community care, NHS secondary care) and EQ-5D were imputed at each time point. Missing EQ-5D was imputed at the individual categorical data domain/response level, an ordered logit model was specified.[54] Pooled estimates were calculated according to Rubin's rules.

Uncertainty surrounding the parameters of interest: incremental costs, QALYs, ICERS, and INMBs were estimated using nonparametric bootstrapping techniques, resampling observations with replacement (1000 replications) giving a bootstrap sample from which 95% CIs were derived with reference to the percentiles at 2.5% and 97.5% for the incremental costs and incremental QALYs.[51] Results were graphically presented in cost-effectiveness planes.[51] Cost-effectiveness acceptability curves (CEACs) were constructed to indicate the probability of the SC intervention being considered cost-effective when added to UC

compared with UC alone for a range of different threshold values of WTP per QALY (£20 000-£30 000 per QALY was used because these are commonly applied ceiling ratios in the United Kingdom). The cost/YFC ICER was compared with the £33 500 to £36 150 threshold range estimated by Kinghorn et al.[55]

A number of sensitivity analyses were performed to explore the robustness of the results (1) using complete cases data set, (2) costs imputed at the total cost level, (3) EQ-5D-5L imputed at the index score level, (4) using SF-6D to generate QALYs, (5) using ICECAP-A to generate YFC, (6) including patient costs (private healthcare and productivity losses), (7) 20% variation around SC intervention costs, and (8) departures from the missing at random hypothesis assumption (Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.09.015).

The current analysis did not include a separate assessment of distributional effects.[56] All analyses were carried out using STATA (V17, Stata Corp).

Results

Resource Use and Costs

Table 1 presents the descriptive mean resource use and associated unadjusted costs per participant over 52 weeks follow-up (for the n = 166 participants with complete cost data), which revealed a total raw difference (NHS + PSS perspective) between the 2 groups of + £894.21, mainly due to the direct delivery of the SC intervention itself. Comparing the NHS primary and community care mean resource use and mean costs between the 2 groups, the differences for specific individual resource use items were not statistically significant

Comparing the secondary care mean resource use and mean costs, none of the differences in individual resource use items reached statistical significance, except for magnetic resonance imaging (MRI) scan costs. More participants in the SC + UC group had MRI scans (25% SC vs 12% UC alone), and also higher than the average number of scans (0.31 vs 0.13) leading to MRI scan costs of £66 and £29 for SC + UC versus UC alone (P = .025). When patients' costs were incorporated, the SC + UC group consistently used fewer resources than the UC-alone group (£1486 SC + UC vs £1740 UC alone), with a total raw difference of −£253.37, although the difference was not statically significant. Overall, no statistically significant differences in the total mean NHS primary care costs and total mean NHS secondary care costs were found, although some evidence that patient costs were lower in the SC + UC group (but nonsignificant). The main driver of differences in costs between the 2 groups would appear to be associated with the direct SC-related intervention cost itself (£1053 per patient). Over 52 weeks, total average unadjusted NHS costs (NHS + patient costs) were £2449 (£2692) and £1555 (£4616) in the SC + UC and UC-alone groups, respectively. Compared with UC, this produced unadjusted NHS costs difference of £894 for the SC + UC intervention. The breakdown of intervention costs per participant is presented in Table 1 and is predominantly driven by the SC consultation sessions delivery costs.

Quality-of-Life Outcomes

The unadjusted mean quality-of-life outcome scores at each time point and mean total QALYs/YFC over 52 weeks are summarized in Table 2 (for participants with complete utility/capability data). At baseline, there was a small, nonsignificant difference in unadjusted EQ-5D and SF-6D scores in favor of the SC + UC group and ICECAP-A scores in favor of the UC group. The mean unadjusted scores for all quality-of-life outcomes at each follow-up were higher in the SC + UC group. Compared with UC alone, a higher unadjusted QALY difference was observed for the SC + UC intervention group (0.0551), but the difference was not statistically significant (P = .1139).

Cost-Utility Analysis

Table 3 presents the base case, adjusted incremental costs, and QALYs and the ICER for SC + UC versus UC alone. The results from the base-case analysis (using the imputed data set) showed that when controlling for baseline covariates, the participants randomized to SC + UC accrued greater incremental costs: £704 (95% CI £605-£807) and greater incremental QALYs: 0.0447 (95% CI 0.0067-0.0826) compared with participants randomized to UC alone. The 95% CIs of the incremental QALYs, which exclude 0/is lacking a negative sign, indicate that the difference is statistically significant. The cost-effectiveness plane/scatter plot (Fig. 1A, B) and Table 3 reveal most cost-effectiveness pairs lying in the north-east quadrant, showing little uncertainty regarding improvement in quality of life associated with the SC + UC intervention. The ICER (£15 765/QALY) is below the conventional £20 000/QALY cost-effectiveness threshold, and the INMB was positive, £189 (95% CI −£574 to £948). Considering the CEAC, SC + UC is the preferred treatment option and suggest a 69% probability of the SC + UC intervention being cost-effective when applying the United Kingdom's lower recommended threshold of £20 000 per QALY (Fig. 1B). However, together, the CEAC and the 95% CIs of the INMB results, which is overlapping, indicate that there is some degree of uncertainty in the results.

Sensitivity Analysis

Several of the results of the sensitivity analysis were generally consistent with the base-case cost-effectiveness findings (Table 4), including when restricted to participants with complete costs and QALYs data, imputing QALYs at the index score level, imputing costs at the total cost level, adopting a broader range of costs, and scenarios with 20% variation around the cost of the SC intervention. However, the results were sensitive to the use of other quality-of-life outcome instruments to measure treatment effectiveness (ie, SF-6D and ICECAP-A vs EQ-5D) (Table 4) and 2 of the 8 scenario analyses exploring departures from the MAR assumption (Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.09.015). Considering the results for YFC, the estimated ICER for SC + UC versus UC alone is £37 082/QALY, which is above the YFC threshold range,[52] and similarly, the ICER using the SF-6D for QALYS is £168 821, well above the £20 000 to £30 000/QALY threshold range.

Cost-effectiveness scatter plots and CEACs for the sensitivity analysis are available in Appendix Figure 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.09.015.

Discussion

Study Findings

The results of this within-trial economic evaluation support and build on the clinical effectiveness evaluation of the MSS3 trial reported in a recently published article.[29] For decision makers applying a WTP cost-effectiveness threshold of £20 000 per QALY gained to judge the cost-effectiveness of competing interventions, the base-case results reveal that adding the SC intervention component to UC is likely to be a more cost-effective strategy (ICER: £15 765; INMB: +£189 [95% CI −£574 to £948], 69% probability of being cost-effective) than UC alone. There was a marked difference in costs and QALYs between the

Table 1. Unadjusted mean resource use and costs per patient over 52 weeks' follow-up (availability of cost data before imputation).

Resource use item	SC + UC (n = 178)				UC alone (n = 176)				Raw between-group differences, SC + UC minus UC alone and *P* values[§]	
	n	Users, *n* (%)	Resource use, mean (SD)	Cost, mean (SD), £	*n*	Users, *n* (%)	Resource use, mean (SD)	Cost, mean (SD), £	Resource use diff	Cost diff
Intervention[*,†]										
erGP training										
Time spent by trainees (total 312 hours)	178		1.75	278.70						
Time spent by trainers (total 104 hours)	178		0.58	92.90						
Tutor preparation time (total 16 hours)	178		0.09	14.29						
erGP ongoing supervision sessions										
Time spent by supervisors (total 30 hours)	178		0.17	26.80						
Time spent by erGPs being supervised (total 30 hours)	178		0.17	26.80						
Intervention delivery[‡]										
Initial session and up to 2/3 follow-up sessions (min)	178		107.68 (43.11)	475.94 (190.0)						
Preparation/review time initial session (min)	178		27.81 (7.83)	73.69 (20.69)						
Preparation/review time final follow-up session (min)	178		24.1 (11.96)	63.87 (26.17)						
Total intervention related costs	178	165 (92.7)	—	£1053.00 (232.45)	176	0 (0)	0 (0)	0 (0)	—	£1053.00, *P* = .0000
NHS primary care										
GP and NHS community services										
GP visits at clinic/surgery	77	48 (62.3)	1.92 (2.44)	78.32 (99.55)	89	58 (65.2)	1.81 (2.09)	73.72 (85.32)	0.11, *P* =.751	4.61, *P* =.751
GP telephone consultations	77	52 (67.5)	3.47 (5.21)	82.77 (124.25)	89	69 (77.5)	3.12 (4.29)	74.56 (102.47)	0.34, *P* =.646	8.21, *P* =.646
GP home visits	77	3 (3.9)	0.06 (0.37)	9.64 (55.63)	89	1 (1.1)	0.01 (0.11)	1.67 (15.73)	0.05, *P* =.227	7.97, *P* =.227
Practice nurse visits at clinic/surgery	77	38 (49.4)	1.12 (1.83)	15.00 (24.55)	89	45 (50.6)	1.45 (3.86)	19.47 (51.82)	−0.33, *P* =.470	−4.47, *P* =.470
Practice nurse telephone consultations	77	18 (23.4)	0.34 (0.70)	1.47 (3.05)	89	15 (16.9)	0.26 (0.67)	1.13 (2.90)	0.08, *P* =.458	0.35, *P* =.458
Practice nurse home visits	77	1 (1.3)	0.03 (0.23)	0.64 (5.64)	89	0 (0)	0 (0)	0 (0)	0.03, *P* =.321	0.64, *P* =.321
Community nurse telephone consultations	77	4 (5.2)	0.09 (0.43)	0.69 (3.75)	89	3 (3.4)	0.04 (0.26)	0.10 (0.94)	0.05, *P* =.418	0.59, *P* =.181
Community nurse home visits	77	2 (2.6)	0.04 (0.25)	0.43 (3.81)	89	0 (0)	0 (0)	0 (0)	0.04, *P* =.181	0.43, *P* =.321
NHS 111/ NHS 24 telephone consultations	77	9 (11.7)	0.19 (0.76)	2.70 (10.55)	89	14 (15.7)	0.29 (0.91)	4.05 (12.56)	−0.10, *P* =.454	−1.35, *P* =.454
Out-of-hours GP service at clinic/surgery	77	3 (3.9)	0.04 (0.19)	3.04 (15.22)	89	5 (5.6)	0.12 (0.62)	9.66 (48.31)	−0.08, *P* =.224	−6.61, *P* =.224
Out-of-hours GP service telephone consultations	77	1 (1.3)	0.01 (0.11)	0.43 (3.76)	89	0 (0)	0 (0)	0 (0)	0.01, *P* =.321	0.43, *P* =.321
Out-of-hours GP service home visits	77	3 (3.9)	0.04 (0.19)	5.99 (29.95)	89	6 (6.7)	0.13 (0.69)	20.73 (106.70)	−0.10, *P* =.215	−14.74, *P* =.215
Walk-in center at clinic/surgery	77	9 (11.7)	0.14 (0.42)	11.70 (34.44)	89	12 (13.5)	0.19 (0.52)	15.65 (42.57)	−0.05, *P* =.510	−3.95, *P* =.510
Other GP and NHS community surgery/clinic visits	77	11 (14.3)	0.27 (0.79)	4.14 (11.97)	89	14 (15.7)	0.40 (1.10)	6.14 (16.77)	−0.13, *P* =.374	−2.00, *P* =.374
Other GP and NHS community telephone consultations	77	12 (15.6)	0.25 (0.80)	2.19 (7.08)	89	13 (14.6)	0.22 (0.58)	2.00 (5.14)	0.02, *P* =.837	0.20, *P* =.841
Other GP and NHS community home visits	77	6 (7.8)	0.17 (0.77)	5.64 (25.65)	89	4 (4.5)	0.13 (0.73)	4.50 (24.25)	−0.03, *P* =.771	1.14, *P* =.771
Other NHS treatments										
Community physiotherapist visits	77	19 (24.7)	0.70 (1.63)	51.29 (119.28)	89	19 (21.4)	0.66 (1.53)	48.59 (111.87)	0.04, *P* =.877	2.81, *P* =.877
Community chiropractor visits	77	0	0	0 (0)	89	2 (2.4)	0.02 (0.15)	1.73 (11.49)	−0.02, *P* =.159	−1.72, *P* =.159

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Table 1. Continued

Resource use item	SC + UC (n = 178)				UC alone (n = 176)				Raw between-group differences, SC + UC minus UC alone and *P* values[§]	
	n	Users, *n* (%)	Resource use, mean (SD)	Cost, mean (SD), £	*n*	Users, *n* (%)	Resource use, mean (SD)	Cost, mean (SD), £	Resource use diff	Cost diff
Community osteopath visits	77	1 (1.30)	0.01 (0.11)	1.00 (8.79)	89	1 (1.1)	0.01 (0.11)	0.87 (8.17)	0.00, *P* =.919	0.14, *P* =.919
Other NHS treatments	77	5 (6.5)	0.29 (1.77)	22.03 (136.36)	89	13 (14.6)	0.27 (0.84)	20.79 64.47)	0.02, *P* =.942	0.05, *P* =.998
Total NHS primary and community care costs	77	71 (92.2)	—	299.13 (348.21)	89	85 (95.5)	—	305.24 (271.93)	—	−6.10, *P* =.9011
NHS secondary care										
Outpatient clinic visits (new)	77	23 (29.9)	0.73 (1.47)	142.08 (288.09)	89	20 (22.5)	0.64 (1.97)	125.12 (384.28)	0.09, *P* =.746	16.96, *P* =.746
Outpatient clinic visits (return)	77	37 (48.1)	1.97 (3.60)	332.13 (606.00)	89	33 (37.08)	1.16 (2.68)	194.72 (451.53)	0.82, *P* =.104	137.41, *P* =.104
Accident and Emergency visits (no admission)	77	16 (20.8)	0.32 (0.77)	79.94 (189.22)	89	16 (18.0)	0.21 (0.51)	52.57 (125.73)	0.11, *P* =.282	27.38, *P* =.282
Elective admission inpatient stays	77	1 (1.3)	0.01 (0.11)	71.73 (629.40)	89	3 (3.4)	0.08 (0.55)	434.39 (3027.90)	−0.07, *P* =.273	266.17, *P* =.273
Non-elective inpatient stays (short stays)	77	0 (0)	0 (0)	0 (0)	89	2 (2.3)	0.02 (0.15)	17.02 (112.89)	−0.02, *P* =.159	−17.20, *P* =.159
Non-elective inpatient stays (long stays)	77	1 (1.3)	0.05 (0.46)	215.80 (1893.67)	89	1 (1.1)	0.07 (0.64)	280.06 (2642.09)	−0.02, *P* =.859	−64.26, *P* =.856
Tests/Investigations										
X-ray	77	24 (31.2)	0.53 (1.12)	15.35 (32.36)	89	26 (29.2)	0.43 (0.78)	12.31 (22.54)	0.11, *P* =.489	3.04, *P* =.489
Ultrasound scan	77	19 (24.7)	0.38 (0.76)	27.48 (55.56)	89	22 (24.7)	0.31 (0.60)	22.95 (43.44)	0.06, *P* =.564	4.52, *P* =.564
MRI	77	19 (24.7)	0.31 (0.59)	66.47 (125.98)	89	11 (12.4)	0.13 (0.38)	28.75 (80.00)	0.18, *P* =.025*	37.72, *P* =.025*
CT scan	77	12 (15.6)	0.19 (0.49)	27.17 (68.03)	89	12 (13.5)	0.21 (0.59)	29.78 (82.71)	−0.02, *P* =.824	−2.61, *P* =.824
Endoscopy	77	4 (5.2)	0.05 (0.22)	13.68 (58.83)	89	5 (5.6)	0.06 (0.23)	14.79 (60.98)	−0.00, *P* =.905	−1.11, *P* =.904
Colonoscopy	77	4 (5.2)	0.10 (0.48)	55.54 (254.09)	89	4 (4.5)	0.04 (0.21)	24.03 (111.39)	0.06, *P* =.316	31.52, *P* =.316
Other tests	77	16 (20.8)	0.48 (1.14)	13.61 (32.37)	89	18 (20.2)	0.47 (1.25)	13.37 (35.50)	0.01, *P* =.963	0.24, *P* =.963
Total NHS secondary care costs	77	57 (74.0)	—	1060.99 (2543.18)	89	64 (71.9)	—	1249.86 (4566.97)	—	−188.86, *P* =.7477
Patient costs										
Private health care treatments										
Physiotherapist visits	77	9 (11.7)	1.05 (4.29)	134.79 (549.10)	89	13 (14.6)	0.79 (2.88)	100.78 (369.28)	0.27, *P* =.646	34.00, *P* =.646
Chiropractor visits	77	4 (5.2)	0.36 (2.03)	15.81 (88.05)	89	7 (7.9)	0.20 (1.12)	8.79 (48.68)	0.16, *P* =.535	7.02, *P* =.535
Osteopath visits	77	1 (1.3)	0.01 (0.11)	0.56 (4.95)	89	8 (9.00)	0.55 (2.43)	23.93 (105.67)	−0.54, *P* =.04*	−23.37, *P* =.04*
Other private health care treatment contacts	77	8 (10.4)	1.38 (6.35)	176.39 (813.83)	89	9 (10.1)	0.72 (2.97)	92.14 (379.99)	0.66, *P* =.407	84.25, *P* =.406
Private tests										
X-ray	77	2 (2.6)	0.03 (0.16)	3.38 (20.81)	89	0 (0)	0 (0)	0 (0)	0.11, *P* =.489	3.38, *P* =.159
Ultrasound scan	77	1 (1.3)	0.01 (0.11)	3.88 (34.07)	89	1 (1.1)	0.01 (0.11)	3.36 (31.69)	0.06, *P* =.564	0.52, *P* =.919
MRI	77	1 (1.3)	0.01 (0.11)	5.19 (45.58)	89	0 (0)	0 (0)	0 (0)	0.01, *P* =.321	5.19, *P* =.321
CT scan	77	1 (1.3)	0.03 (0.23)	15.25 (133.79)	89	0 (0)	0 (0)	0 (0)	−0.02, *P* =.824	15.25 *P* =.321
Endoscopy	77	0 (0)	0 (0)	0 (0)	89	2 (2.3)	0.02 (0.15)	50.90 (337.60)	−0.00, *P* =.905	−50.90, *P* =.159
Colonoscopy	77	1 (1.3)	0.01 (0.11)	32.66 (286.61)	89	0 (0)	0 (0)	0 (0)	0.06, *P* =.316	32.66, *P* =.321
Other tests	77	0 (0)	0 (0)	(0)	89	2 (2.3)	0.02 (0.15)	2.92 (19.38)	0.01, *P* =.963	−2.92, *P* =.159
Total private health care costs	77	6 (7.8)	-	387.91 (1012.05)	89	3 (3.4)	-	282.82 (745.88)		−105.09, *P* =.4536
Time/productivity losses due to illness (days)										
Paid employment	77	31 (40.3)	9.73 (30.80)	1087.92 (3323.82)	89	44 (49.4)	10.72 (22.71)	1269.94 (2925.11)	−0.99, *P* =.816	−182.01, *P* =.711

continued on next page

Table 1. Continued

Resource use item	SC + UC (n = 178)				UC alone (n = 176)				Raw between-group differences, SC + UC minus UC alone and *P* values[§]	
	n	Users, *n* (%)	Resource use, mean (SD)	Cost, mean (SD), £	*n*	Users, *n* (%)	Resource use, mean (SD)	Cost, mean (SD), £	Resource use diff	Cost diff
Unpaid employment	77	2 (2.6)	0.08 (0.58)	9.00 (66.91)	89	3 (3.4)	0.87 (6.54)	99.88 (754.83)	−0.79, *P* =.261	−90.88, *P* =.261
Education / training	77	1 (1.3)	0.03 (0.23)	1.48 (12.98)	89	4 (4.5)	1.53 (8.28)	87.04 (471.83)	−1.50, *P* =.091	−85.56, *P* =.091
Total productivity losses related costs		33 (42.9)	-	1098.40 (3329.02)		48 (53.9)	-	1456.85 (3004.22)		−358.45, *P* =.4703
Total patient costs	77	43 (55.8)	-	1486.30 (3461.67)	89	54 (60.7)	-	1739.67 (3346.35)	-	−253.37, *P* =.633
Total NHS costs	77	-	-	2449.30 (2691.87)	89	-	-	1555.09 (4616.10)	-	894.21, *P* =.1237
Total costs, including patient costs	77	-	-	3935.61 (4439.72)	89	-	-	3294.76 (5981.54)	-	640.84, *P* =.4307

A&E indicates Accident and Emergency (department); CN, community nurse; erGP, extended-role general practitioner; GP, general practitioner; HCP, healthcare professional; NHS, National Health Service; PN, practice nurse.
*Includes time spent by the erGPs (the trainees) on tasks and activities related to receiving training, intervention delivery, preparation and reviewing sessions, receiving ongoing supervision sessions, and time spent by the GP trainers on tasks and activities related to training to erGPs, conducting ongoing supervision sessions, and tutor preparation.
†Including the 13 participants allocated to the intervention group that did not receive any sessions.
‡Sum of erGP time (in minutes) on preparing, delivering, and reviewing the SC intervention sessions; missing erGP session time was imputed using mean imputation. erGP indicates extended-role GP; SC, symptoms clinic; UC, usual care;.
§Comparison of the mean resource use and mean costs between the 2 groups using independent two-sample Student's *t* test with reported statistical significance for differences. HCRU indicates healthcare resource utilization.

2 treatment options, with SC + UC producing statistically greater health-related QoL benefits but higher healthcare and societal costs than UC alone in the base case. Notably however, the sensitivity analyses revealed a significant increase in the ICERs when using the SF-6D and ICECAP-A for QoL utility to estimate QALYs/YFC compared with when using the EQ-5D-5L (ie, £184 724 vs £40 772 vs £15 765 per QALY, respectively). This was largely due to the significantly smaller QALY/YFC gains (ie, 0.0038 and 0.0173, respectively) generated with these 2 outcome measures compared with the QALYs gained using the EQ-5D-5L (ie, 0.0447, the preferred instrument by UK's NICE).

Table 2. Unadjusted mean quality-of-life score per participant over 52 weeks' follow-up (before imputation, availability of QoL data).

	SC + UC (n = 178)	UC alone (n = 176)	Raw between-group mean difference	*P* value[†]
EQ-5D-5L, *n*; mean (SD)*				
Baseline	178; 0.5833 (0.2430)	176; 0.5602 (0.2504)	0.0231	.3782
13 weeks	144; 0.5546 (0.2733)	129; 0.5025 (0.2842)	0.0523	.1236
26 weeks	137; 0.5492 (0.2887)	130; 0.5064 (0.2889)	0.0428	.2274
52 weeks	130; 0.5589 (0.2796)	128; 0.4801 (0.2999)	0.0788	.0300
Total QALYs over 52 weeks	113; 0.5632 (0.2530)	110; 0.5080 (0.2653)	0.0551	.1139
SF-6D utility score, *n*; mean (SD)				
Baseline	176; 0.5766 (0.1076)	175; 0.5711 (0.1012)	0.0055	.6228
26 weeks	139; 0.6139 (0.1315)	125; 0.5904 (0.1172)	0.0235	.1258
52 weeks	127; 0.6206 (0.1394)	117; 0.5820 (0.1094)	0.0386	.0164
Total QALYs over 52 weeks	117; 0.6122 (0.1157)	105; 0.5899 (0.1016)	0.0223	.1284
ICECAP-A, *n*; mean (SD)				
Baseline	178; 0.7244 (0.1739)	176; 0.7314 (0.1841)	−0.0070	.7135
26 weeks	142; 0.7388 (0.1755)	128; 0.7289 (0.1928)	0.0099	.6618
52 weeks	133; 0.7564 (0.1946)	128; 0.7210 (0.2100)	0.0354	.1592
Total years of full capability over 52 weeks	125; 0.7426 (0.1613)	115; 0.7353 (0.1851)	0.0073	.7448

ICECAP-A indicates capability measure for adults; QALY, quality-adjusted life year; SF-6D, Short Form-Six Dimensions; SC, Symptoms Clinic (intervention); UC, usual care.
*Crosswalk health utility score.[45,46]
†Comparison of the mean outcomes: EQ-5D-5L/SF-6D/ICECAP-A and mean QALYs/YFC between the 2 groups using the independent two-sample Student's *t* test with reported statistical significance for differences.

Table 3. Adjusted* mean incremental costs, mean incremental QALYs, and incremental cost-effectiveness ratio over 52 weeks between groups.

Base-case analysis, imputed data, n = 354 (NHS + PSS perspective)§	Total costs, mean (95% CI), £*	Total QALYs, mean (95% CI)*	Incremental costs, mean (95% CI), £†, ‡	Incremental QALYs, mean (95% CI)†, ‡	ICER, £/QALY	Distribution CE-plane (%)‖				Incremental NMB, mean (95% CI) at:		Probability of cost-effectiveness at:	
						NE	SE	SW	NW	£20 000 per QALY threshold	£30 000 per QALY threshold	£20 000 per QALY threshold	£30 000 per QALY threshold
SC + UC	2302.53 (2214.09, 2394.76)	0.5826 (0.5533, 0.6080)	704.35 (605.30, 807.00)	0.0447 (0.0067, 0.0826)	15 765	99.1	0	0	0.9	189.22 (−573.62, 948.28)	636.00 (−502.97, 1770.30)	68.8	86.7
UC alone	1597.83 (1533.01, 1640.13)	0.5380 (0.5093, 0.5654)											

ICER indicates incremental cost-effectiveness ratio; NHS, National Health Service; PSS, Personal Social Services; QALY, quality-adjusted life-year; SC, Symptoms Clinic (intervention); UC, usual care. NMB, Incremental net monetary benefit (calculated as incremental benefit × threshold £20 000/£30 000) − incremental cost. Incremental NMB measures the difference in NMB between alternative interventions, a positive incremental NMB indicating that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.

*Adjusted for baseline differences/covariates (age, gender, baseline PHQ-15 score, baseline EQ-5D utility score).

†Bootstrapped nonparametric 95% CI (2.5th, 97.5th percentile). Generalized linear model with Poisson distribution and power −0.65 link function to estimate incremental costs and generalized linear model with Poisson distribution and power 0.7 link function to estimate incremental QALYs.

‡Compared with usual care.

§Imputed data set (m = 60).

‖The C-E plane is divided into 4 quadrants: the proportion/distribution of cost-effectiveness pairs from the plot of incremental costs (y-axis) and benefits (x-axis) lying in (1) the north-east (NE) quadrant, the SC intervention generates more QALYs but is more costly; (2) south-east (SE) quadrant, SC intervention generates more QALYs and is less expensive; (3) south-west (SW) quadrant, the SC intervention generates less QALYs but is less expensive; (4) north-west quadrant (NW), the SC intervention generated less QALYs and is more expensive.

Comparison With Other Economic Evaluation Studies

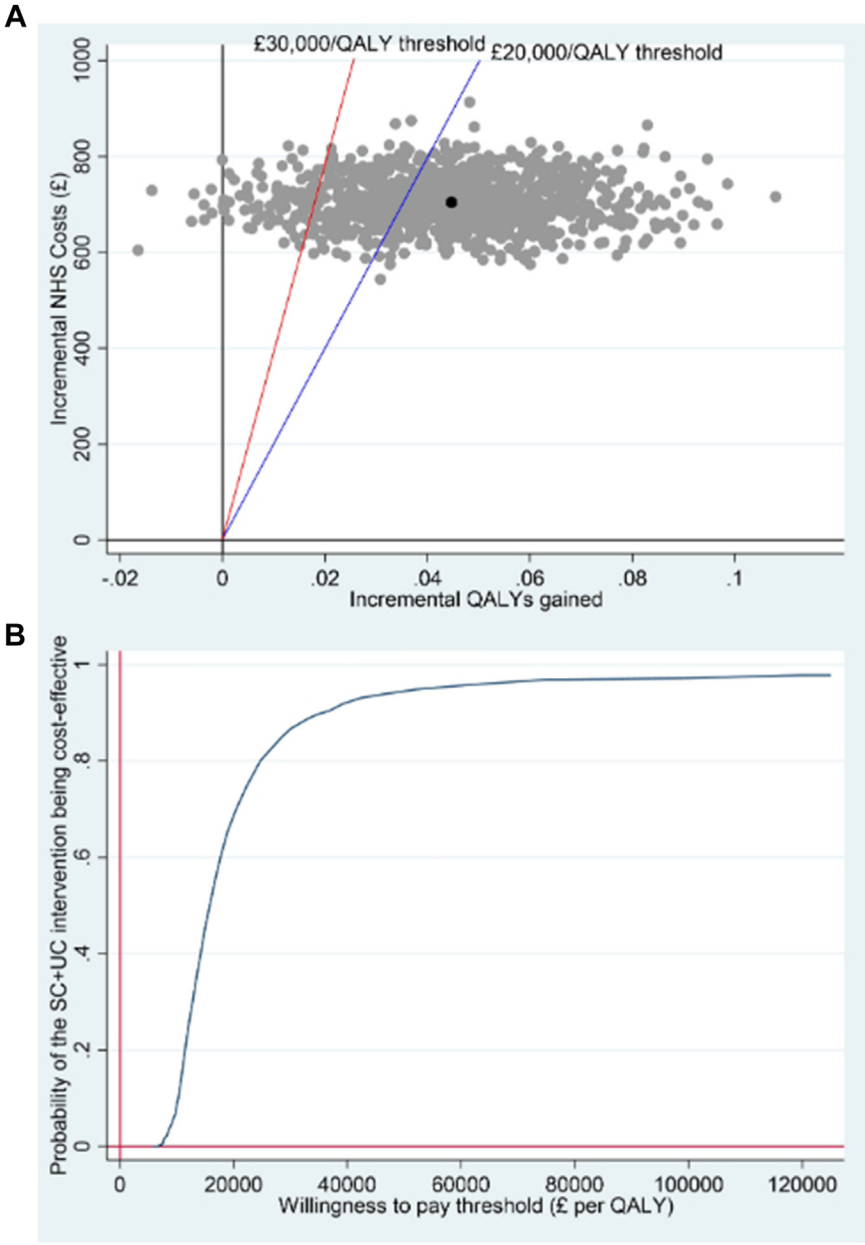
The MSS3 trial was original in using an extended medical consultation model focused on explanation. Thus, comparisons are limited to studies of psychologist or nurse specialist–delivered interventions for persistent physical symptoms (often using the older term "medically unexplained symptoms"). Taking this broader perspective, systematic reviews have found relatively few that included economic evaluations. Konnopka et al[8] identified 8 economic evaluations, of which only 2 were cost-effectiveness analyses. Wortman et al[57] included studies of interventions for specific syndromes in addition to heterogeneous persistent physical symptoms. They identified 5 studies involving patients with medically unexplained symptoms, of which 4 were group interventions and 1 was an individual treatment randomized controlled trial of brief interpersonal therapy.[58] Although clinically effective, this was not cost-effective with an estimated ICER of 41 840 Euro per QALY. More recently, a primary care–based study from The Netherlands examined cognitive behavioral therapy (CBT) delivered by mental health nurse practitioners for nonspecific persistent physical symptoms.[59] The intervention was associated with minimal change in QALYs, mean difference 0.01 (95% CI −0.01 to 0.04), but lower healthcare costs, mean difference −2300€ (95% CI −3257 to −134). Finally, a third review[17] focused on interventions relevant to the UK setting found only 2 economic evaluations, neither of which included a heterogeneous group of patients with persistent physical symptoms.

A number of studies have reported healthcare use after interventions as an outcome without formal economic analysis. These were reviewed by Jones and de C Williams[21] who concluded that CBT showed weak benefits in reducing healthcare use in people with medically unexplained symptom and that this was limited to healthcare contacts and medication use and did not affect medical investigations or healthcare costs.

Strengths and Limitations

The economic evaluation alongside the MSS3 trial is, to our knowledge, the first economic evaluation to assess the value added by an erGP-led SC intervention to UC (vs UC alone) in patients with persistent physical symptoms delivered in the primary care setting. This study is associated with some potential limitations. First, because of the large proportion of missing data, there remains some level of uncertainty in the results. Our rates of missing data are marginally higher than the range of those reported in a recent review of missing data in economic evaluations[60]: with studies reporting average 37% (range 19%-53%) of participants having missing cost-effectiveness data, 21% missing cost data (range 8%-33%), and 27% missing effectiveness data (range 14%-45%). The comparative proportions of MSS3 trial missing data were 198 of 354 (56%), 188 of 354 (53%), and 131 of 354 (37%), respectively. However our results were found to be generally robust using alternative scenarios about the missing data mechanism, except for 2 scenarios in which the ICER exceeded £20 000 per QALY (Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.09.015) Second, higher healthcare costs with SC + UC were driven by the intervention related costs. It is possible that a lower intervention cost, more reflective of future resource use in a steady state after longer term rollout of the SC intervention, would be achievable (eg, with erGP training/supervision costs expected to be reduced). A lower intervention cost estimate was explored as a sensitivity analysis and showed that the cost-effectiveness of the SC intervention improved. Third, and related to this latter point, extrapolation beyond the 12-month trial period to estimate long term clinical effectiveness and cost-effectiveness was not undertaken as part of this funded trial economic evaluation study. Thus, to reduce decision uncertainty, we recommend that future estimates of the cost-effectiveness of the SC intervention in the primary care setting be assessed for a follow-up period greater than 1 year, eg, over 2 or 5 years, to test the maintenance of QoL improvements

Figure 1. Cost-effectiveness plane (A) and cost-effectiveness acceptability curve (CEAC) (B) for the base-case analysis, NHS and PSS perspective (SC + UC vs UC alone), imputed data set.



NHS indicates National Health Service; QALY, quality-adjusted life-year; SC, Symptoms Clinic (intervention); UC, usual care.

obtained at 12 months, using cost-effectiveness using decision-analytic modeling approaches[61] involving synthesizing evidence from a range of different sources. We also acknowledged this in the main trial effectiveness article,[28] although as we noted there, at least some ongoing benefit is likely given that the between-group difference increased in favor of the intervention between 6 and 12 months after enrollment.

Fourth, healthcare use is likely to have been affected by the Covid-19 pandemic, which reduced use of primary care for a short period in the second quarter of 2020 but also precipitated changes in the way care was delivered. The suspension of much nonurgent elective care in hospitals through repeated pandemic waves may also have led to reduced rates of consultation, referral, and testing for at least some symptoms. Although in normal circumstances up to half of referrals result in no diagnosis,[2] this proportion may have been lower during much of this study. Although this is unlikely to have had differential effects between allocation arms of the study, a reduction in the total volume and a tightening of eligibility criteria to restrict access for those patients least likely to have serious disease may have reduced the study's power to demonstrate an effect.

Finally, the consequences of the pandemic for access to healthcare premises affected our method of data collection. Our

Table 4. Sensitivity analysis: adjusted mean incremental costs, incremental effectiveness (QALY), and incremental cost-effectiveness ratio over 52 weeks between groups.

Analysis	Incremental costs, mean (95% CI), £[†,‡]	Incremental QALYs, mean (95% CI)[†,‡]	ICER, £/QALY	Distribution CE-plane (%)[††]				Incremental NMB, mean (95% CI) at:		Probability of cost-effectiveness at:	
				NE	SE	SW	NW	£20 000 per QALY threshold	£30 000 per QALY threshold	£20 000 per QALY threshold	£30 000 per QALY threshold
Base case, imputed cases data set, imputing at the main cost category level (NHS primary and community care, secondary care), NHS and PSS perspective, (NHS and PSS perspective*	704.35 (605.30, 807.00)	0.0447 (0.0067, 0.0826)	15 765	99.1	0	0	0.9	189.22 (−573.62, 948.28)	636.00 (−502.97, 1770.30)	68.8	86.7
Complete cases data set (NHS + PSS perspective)[§]	913.52 (721.06, 1111.20)	0.0616 (0.0066, 0.1142)	14 833	98.7	0	0	1.3	318.19 (−783.49, 1400.85)	934.05 (−730.81, 2518.02)	72.6	87.6
Costs imputed at the total cost level, (NHS and PSS perspective)	662.57 (568.00, 748.14)	0.0447 (0.0067, 0.0826)	14 830	99.1	0	0	0.9	230.99 (−527.66, 966.57)	677.77 (−462.08, 1787.96)	72.7	87.7
QALYs imputed at the EQ-5D utility index score level (versus QALYs imputed at the individual HR-QoL domain level as in the base case), (NHS + PSS perspective)	704.35 (605.30, 807.00)	0.0548 (0.0128, 0.0952)	12 842	99.8	0	0	0.2	392.62 (−450.55, 1251.74)	941.10 (−316.51, 2184.24)	83.6	93.4
Cost of intervention + 20%, (NHS + PSS perspective)[‖]	892.02 (781.28, 993.06)	0.0447 (0.0067, 0.0826)	19 943	99.1	0	0	0.9	2.55 (−759.21, 770.14)	449.33 (−696.70, 1598.99)	51.4	78.3
Cost of intervention −20%, (NHS + PSS perspective)[‖]	567.27 (478.71, 658.66)	0.0447 (0.0067, 0.0826)	12 697	99.1	0	0	0.9	326.29 (−426.44, 1076.54)	773.07 (−333.53, 1884.62)	80.8	90.9
Using SF-6D utility score, (NHS + PSS perspective)[‖]	704.35 (605.30, 807.00)	0.0038 (−0.0145, 0.0218)	184 724	65.0	0	0	35.0	−628.09 (−998.37, −228.32)	−589.96 (−1127.06, −12.38)	0.0	2.2
Using ICECAP-A utility score, (NHS + PSS perspective)[‖]	704.35 (605.30, 807.00)	0.0173 (−0.0123, 0.0460)	40 772	88.0	0	0	12.0	£33 500 per YFC −125.62 (−1,120.77, 849.54)	£36 150 per YFC −79.84 (−1,152.27, 9721.34)	£33 500 per YFC 40.4	£36 150 per YFC 44.4
Including private health care and productivity losses costs (NHS + PSS and patient cost perspective)[‖,**]	524.953 (333.67, 703.82)	0.0447 (0.0067, 0.0826)	11 740	99.1	0	0	0.9	369.03 (−411.70, 1116.93)	815.81 (−347.05, 1938.32)	81.6	92.1

ICER indicates incremental cost-effectiveness ratio; NHS, National Health Service; QALY, quality-adjusted life year; SC, Symptoms Clinic (intervention); UC, usual care.
*Adjusted for baseline covariates (age, gender, baseline PHQ-15 score, and baseline utility score)
[†]Bootstrapped nonparametric 95% CI (2.5th, 97.5th percentile). Generalized linear model with Poisson distribution and power −0.65 link function to estimate incremental costs and generalized linear model with Poisson distribution and power 0.7 link function to estimate incremental QALYs.
[‡]Compared with usual care.
[§]156 complete cases were included – UC alone (n = 84) and SC + UC (n = 72). For the adjusted analysis, complete cases are without any missing data on cost and health utility at each time point.
[‖]Imputed data set (m = 60)
**Generalized linear model with Gaussian family distribution and an identity link function to estimate incremental costs and generalized linear model with Poisson family distribution with power 0.7 link function to estimate incremental QALYs estimated.
[††]The C-E plane is divided into 4 quadrants: the proportion/distribution of cost-effectiveness pairs from the plot of incremental costs (y-axis) and benefits (x-axis) and presented as a scatterplot of the point estimates obtained as a result of the 1000 runs depicted in 4 quadrants, summarized as follows: 1. North-west (upper-left) quadrant—the SC + UC intervention is dominated by UC alone. The SC + UC intervention is more costly and less effective than UC alone. 2. North-east (upper-right) quadrant—further evaluation required. The SC + UC intervention is more costly and more effective than UC alone. The ICER is computed to assess whether the net incremental health gain is worth the incremental cost. 3. South-west (lower-left) quadrant—further evaluation required. The intervention is less costly and less effective than UC alone. The ICER is computed to assess whether the cost saving is worth the net incremental health loss. 4. South-east (lower-right) quadrant—the SC + UC intervention is dominant compared with UC alone and unambiguously preferred to usual care. The intervention is less costly and more effective than usual care.

original plan was to extract healthcare resource use from GP records, with participant self-report as a back-up. However, this became extremely difficult because of access to GP surgeries during the pandemic; therefore, self-report data have been used in all analyses. This affected our collection of information on prescribed information, which was originally intended to be extracted from the GP record system. Thus, the medication section of the self-report form was kept fairly brief to minimize participant burden. However, medication use was not an important outcome in this study because there are no guideline-

indicated medicines recommended for heterogeneous persistent physical symptoms.

Conclusions

This study provides new economic evidence for investing in primary care–based SC interventions to improve the common problem of persistent physical symptoms. Decision makers may judge that an extended GP consultation model generates greater health-related QoL gains than UC alone. Furthermore, using commonly accepted WTP for QALY gain thresholds, the addition of a SC to UC is likely to provide a cost-effective use of healthcare resources. To reduce decision uncertainty, we recommend that future studies of the cost-effectiveness of SC intervention strategies be based over a longer time horizon than the trial.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material section.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2024.09.015.

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