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Clinical and cost-effectiveness of the Lightning Process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial

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CORRECTION NOTICE

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ABSTRACT

Objective Investigate the effectiveness and cost-effectiveness of the Lightning Process (LP) in addition to specialist medical care (SMC) compared with SMC alone, for children with chronic fatigue syndrome/myalgic encephalitis (CFS/ME).

Design Pragmatic randomised controlled open trial. Participants were randomly assigned to SMC, or SMC plus the LP (SMC+LP). Randomisation was minimised by age and gender.

Setting Specialist paediatric CFS/ME service.

Patients Aged 12–18 years with mild/moderate CFS/ME.

Main outcome measures The primary outcome was the SF-36 physical function subscale (PFS) at 6 months. Secondary outcomes included the SF-36-PFS at 3 and 12 months, and pain, anxiety, depression, school attendance and cost-effectiveness from a health service perspective at 3, 6 and 12 months.

Results We recruited 100 participants between September 2010 and September 2013. We tested the feasibility of running the trial with a feasibility phase (29 September 2010 to 18 September 2012). The full trial was registered in June 2012 when we had determined it was a feasible study. Of the 100 participants, 51 were randomised to SMC+LP. Data from 81 participants were analysed at 6 months. Physical function (SF-36-PFS) was better in those allocated SMC+LP (adjusted difference in means 12.5 [95% CI 4.5 to 20.5], $p=0.003$) and this improved further at 12 months (15.1 [95% CI 5.8 to 24.4], $p=0.002$). At 6 months, fatigue and anxiety were reduced and at 12 months, fatigue, anxiety, depression and school attendance had improved in the SMC+LP arm. Results were similar following multiple imputation. SMC+LP was more cost-effective in the multiple imputation data set (difference in means in net monetary benefit at 12 months £1474 [95% CI £111 to £2836], $p=0.03$) but not for complete cases.

Conclusion The LP is effective and is probably cost-effective when provided in addition to SMC for mild/moderately affected adolescents with CFS/ME.

Trial registration number ISRCTN81456207.

INTRODUCTION

Paediatric chronic fatigue syndrome (CFS) or myalgic encephalitis (ME) affects 0.57%–2.4%^{1–4} of

What is already known on this topic?

- Paediatric chronic fatigue syndrome/myalgic encephalitis (CFS/ME) is relatively common with a negative impact on school, mood and quality of life.
- Even with effective treatment, a significant number of children have not recovered at 6 months.
- The Lightning Process (LP) is used by children with CFS/ME in the UK but with no evidence of effectiveness.

What this study adds?

- At 6 months, children who received LP in addition to specialist medical care (SMC) had better physical function, fatigue and less anxiety.
- At 12 months, children who received LP in addition to SMC had better fatigue, anxiety, depression and school attendance.
- Adding LP is probably cost-effective but not all children wish to take part.

children and is disabling with important impacts on mood,^{5 6} school attendance,^{4 7 8} quality of life⁹ and family functioning.¹⁰ It is defined as generalised fatigue causing disruption of daily life, persisting after routine tests, and investigations have failed to identify an obvious underlying cause.¹¹ A minimum of 3 months of fatigue is required before the diagnosis can be made.¹² On average, those affected miss a year of school overall and half are bedbound at some stage.^{13 14}

There is a limited evidence base for treatment of paediatric CFS/ME.^{12 15 16} Three randomised trials have shown that cognitive-behavioural therapy (CBT) delivered individually,¹⁷ with biofeedback¹⁸ or via the internet¹⁹ is effective at 6 months compared with waiting list or usual medical care. All three studies reported improvements in fatigue,

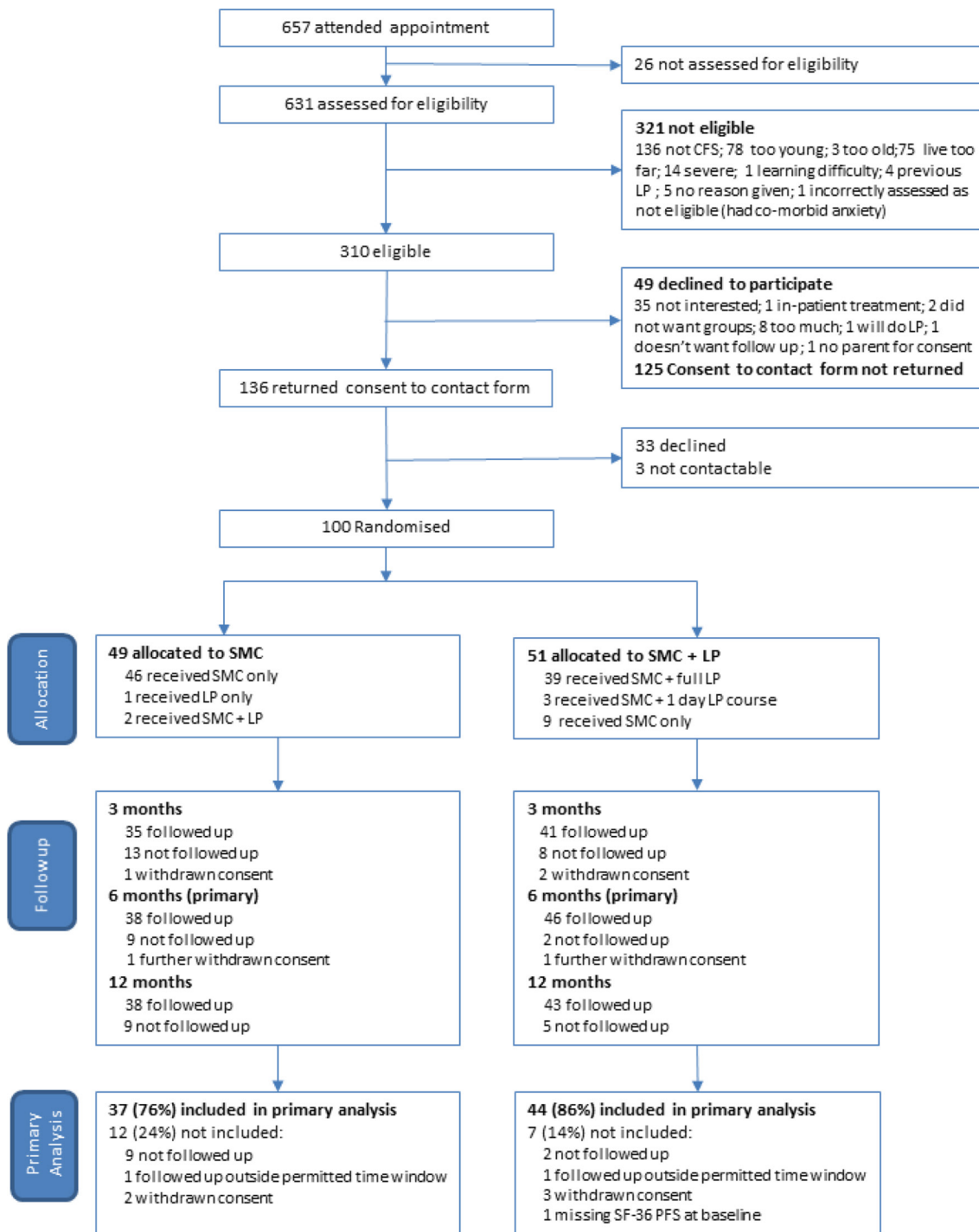


Figure 1 Specialist Medical Intervention and Lightning Evaluation (SMILE): Consolidated Standards of Reporting Trials (CONSORT) trial profile. CFS, chronic fatigue syndrome; LP, Lightning Process; PFS, physical function subscale; SMC, specialist medical care.

school attendance and a reduction in disability. Family-focused CBT appears to be as effective as psychoeducation in terms of school attendance at 6 months and recovery at 24 months.^{20 21} However, even with effective treatment, over a third of children^{19 20} have not recovered at 6 and 12 months^{20 21} and 21%²¹–36%²² are still unwell (eg, attending school less than 70% of the time) at 24 months. There is therefore an urgent need to find more effective treatments.

The Lightning Process (LP) is developed from osteopathy, life coaching and neurolinguistic programming and is used for

a variety of conditions including CFS/ME. Clients read information, attend three group sessions and then receive follow-up phone calls.²³ More than 250 children use LP for their CFS/ME each year in the UK (at a cost of ~£620 each), but there are no reported studies investigating its effectiveness, cost-effectiveness or side effects. Having shown that recruitment, randomisation and data collection were feasible and acceptable²⁴ we conducted a randomised trial to investigate the effectiveness and cost-effectiveness of LP in addition to specialist medical care (SMC), compared with SMC alone, for children with CFS/ME.

Table 1 Characteristics of the randomised participants at baseline

	SMC group		SMC+LP group	
	n		n	
Demographic characteristics				
Mean age (SD)	14.5 (1.6)	49	14.7 (1.4)	51
Female, n (%)	38 (78)	49	38 (75)	51
Median months from onset of illness to baseline assessment (25th percentile, 75th percentile)	12 (7.0, 22.0)	49	12 (8.0, 18.0)	49
Clinical characteristics				
Mean SF-36 physical function score* (SD)	56.0 (21.5)	49	53.0 (18.8)	50
Mean Chalder Fatigue score† (SD)	25.1 (4.2)	49	25.0 (4.2)	50
Mean pain VAS† (SD)	42.4 (29.4)	48	51.6 (28.5)	48
Mean SCAS† (SD)	40.3 (20.1)	48	29.8 (16.9)	49
Mean HADS anxiety score† (SD)	10.4 (4.4)	48	8.8 (4.5)	51
Mean HADS depression score† (SD)	8.1 (4.4)	48	7.5 (3.1)	50
Mean EQ-5D score* (SD)	0.34 (0.36)	49	0.31 (0.34)	51
School attendance in the previous week, n (%)				
None	7 (14%)	49	6 (12%)	50
0.5 day	7 (14%)	49	5 (10%)	50
1 day	3 (6%)	49	3 (6%)	50
2 days	8 (16%)	49	8 (16%)	50
3 days	12 (24%)	49	12 (24%)	50
4 days	9 (18%)	49	12 (24%)	50
5 days	3 (6%)	49	4 (8%)	50

All results rounded to 1 decimal point or whole percentage points.

*Higher score=fewer symptoms, better function.

†Higher score=more symptoms, poorer function.

HADS, Hospital Anxiety and Depression Scale; LP, Lightning Process; SCAS, Spence Children's Anxiety Scale; SF-36, 36-item Short-Form health survey; SMC, specialist medical care; VAS, visual analogue scale.

METHODS

Study design and participants

A detailed description of the study protocol has been reported.²⁵ Between September 2010 and September 2013 we recruited participants after clinical assessment by the Bath/Bristol paediatric CFS/ME service, a large regional and national National Health Service (NHS) specialist service. We tested the feasibility of running this trial with a feasibility phase (29 September 2010 to 18 September 2012). We determined the trial was feasible in June 2012 and registered the full trial (31 July 2012). We applied for an amendment to recruit children into the full trial as opposed to a feasibility trial (see online supplementary table 1 for detailed description of amendments). Full trial first randomisation was on 19 September 2012. We continued seamlessly with participant recruitment without any interim between-group comparison of participant outcome data from the feasibility phase. Children from both phases (feasibility and full) were analysed. Children were diagnosed with CFS/ME after a thorough assessment which included screening for other disorders associated with fatigue.¹² Baseline data were collected at this assessment. Children were eligible if they had CFS/ME, were aged 12–18, spoke English and were not housebound.

Randomisation and masking

Allocation to trial arms was in equal proportions using minimisation by age (12–15/16–18 years) and gender, weighted towards minimising the imbalance in trial arms with probability 0.8. Allocation was concealed using a telephone-based interactive voice response system, created and maintained by the Bristol Randomised Trials Collaboration and accessed by the recruiting researcher. This was an open study: the randomised

intervention was conveyed after obtaining consent, during the recruitment interview so that participants, parents, therapists and researchers were aware of treatment allocation. Data analyses were conducted using masked treatment codes.

Interventions

All participants were offered SMC¹² which focused on improving sleep and using activity management to establish a baseline level of activity (school, exercise and social activity) which is then gradually increased. Sessions were delivered by a range of professionals including doctors, psychologists, physiotherapists and occupational therapists in family-based rehabilitation consultations. Follow-up sessions were either face to face or by telephone. The number and timing of the sessions were agreed with the family depending on each adolescent's needs and goals. Those with significant anxiety or low mood were offered additional CBT. Participants could choose to use physiotherapist-delivered graded exercise therapy (GET), which provides detailed advice about exercise and focuses on an exercise programme rather than other activities.

Participants randomised to SMC+LP were asked to read information about LP and complete an assessment form with their parents to identify their goals and describe what they had learnt. They then had a telephone call with an LP practitioner (online supplementary appendix 1) to discuss attending an LP course consisting of three 4-hour sessions on consecutive days run with groups of two to five young people. Each had a theory session with taught elements on the stress response, how the mind and body interact and how thought processes can be either helpful or negative. This was followed by group discussion where the language used was discussed and in some cases

challenged, and where participants were encouraged to think about what they could take responsibility for and change. In the practical session, participants identified a goal they wished to achieve (such as standing for longer) and were given different cognitive (thinking) strategies before and while the goal was attempted. They were also asked to identify a goal to attempt at home. After the course, young people were offered at least two follow-up phone calls with an LP practitioner.

Outcomes

The primary outcome was the SF-36 physical function subscale (SF-36-PFS)²⁶ analysed as a continuous variable collected at 6 months after randomisation. We chose the SF-36 based on qualitative work conducted in the feasibility phase of the study.²⁴ We have reported that parents and participants 'commented that the school attendance primary outcome did not accurately reflect what they were able to do, particularly if they were recruited during, or had transitioned to, A levels during the study.' In addition, 'we were aware of some participants who had chosen not to increase school attendance despite increased activity.' We therefore concluded that: 'trials involving 17 and 18 year olds should consider alternative primary outcome measures to school attendance as it is difficult to assess for those transitioning from General Certificate of Secondary Education to A levels, and may not be appropriate for those who do not consider school attendance their primary goal.' At this stage, our recommendation was that a 'full study uses other primary outcomes, such as the SF-36 or the Chalder Fatigue Scale and uses school attendance as a secondary outcome.' These findings informed our application for our ethical amendment to a full study in 2011 (see online supplementary table 1) and were published in our feasibility paper in 2013.²⁴

Qualitative interviews with Specialist Medical Intervention and Lightning Evaluation (SMILE) participants then formed part of a larger study which described the conceptual model for paediatric CFS/ME.²⁷ In this study, physical activity (or disability) is described by children as being pivotal because of the impacts on social participation and emotional well-being. While school was deemed to be an important contextual factor, these qualitative results led us to choose the SF-36-PFS as a primary outcome with school attendance as a secondary outcome. There was no analysis of any outcome data during or after the feasibility phase until the entire trial was completed.

Secondary outcomes were the SF-36-PFS at 3 and 12 months, and school attendance (days per week), the Chalder Fatigue Scale,²⁸ pain (visual analogue scale), Hospital Anxiety and Depression Scale (HADS),²⁹ Spence Children's Anxiety Scale (SCAS)³⁰ and quality-adjusted life-years (QALY, derived from the EQ-5D-Y)³¹ at 3, 6 and 12 months. At 3, 6 and 12 months parents completed an adapted four-item Work Productivity and Activity Impairment: General Health questionnaire (V2.0)³² and a resource use questionnaire assessing their child's health service use (eg, general practitioner or specialist care), educational service use (eg, school counsellor), health-related travel and other family costs.

Time windows for questionnaire return were prespecified as 6 weeks after the 3-month follow-up, 6 weeks before or up to 3 months after the 6-month follow-up, and 3 months before or after the 12-month follow-up. Those who had not responded within 1 week were sent a reminder letter with a reduced set of questionnaires (SF-36-PFS, Chalder Fatigue Scale and school attendance). From February 2011 non-responders were telephoned by a researcher and the SF-36-PFS and Chalder Fatigue Scale were completed over the phone to improve follow-up rates.

Sample size

A consensus definition for a small clinically important difference on the SF-36-PFS at 6 months' follow-up is 10 points.³³ However, we did not want to miss a smaller but still potentially important effect of as low as 8 points. To detect a between-group difference of 8–10 points with 90% power, 1% two-sided significance and SD of 10 requires between 32 and 50 participants per group for analysis. Allowing for 10%–20% non-collection of primary outcome data, we aimed to recruit between 80 ($32 \times 2/0.8$) and 112 ($50 \times 2/0.9$) participants.

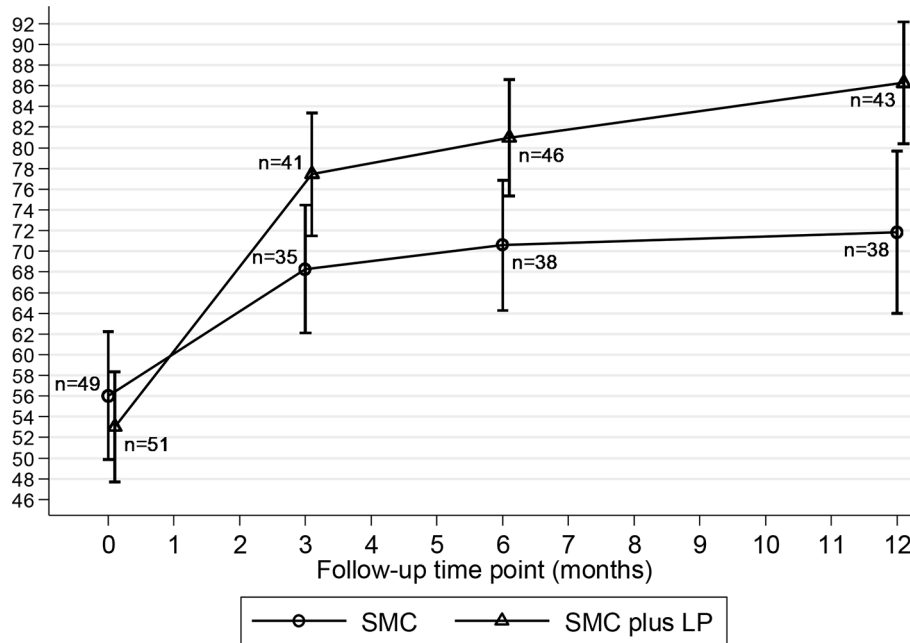
Statistical analysis

The statistical analysis plan was agreed by the study management group and published on our website prior to analyses. The primary analysis compared mean SF-36-PFS scores at 6 months according to randomised allocation among participants with measured outcomes, using multivariable linear regression adjusting for baseline values of the outcome, baseline age and gender. Similar regression analyses were conducted for secondary outcomes. Sensitivity analyses of the primary outcome adjusted for variables for which there was baseline imbalance; excluded those recruited up to 31 January 2011 preceding the protocol amendment to allow collection of follow-up data by phone; and used multiple imputation of missing data. Missing items in partially completed scales (Chalder Fatigue and SF-36-PFS) or subscales (SCAS and HADS anxiety and depression) were imputed using the mean of completed items, if only one item (or two for the SCAS subscales) was missing. If more items were missing the whole scale or subscale was scored as missing. We conducted a repeated measures analysis using all follow-up SF-36-PFS scores, with and without an interaction between allocation arm and time, to investigate whether between-group differences remained constant over time. We did not analyse 3-month outcomes except in this repeated measures analysis for SF-36-PFS as these were unlikely to be informative since the primary follow-up was at 6 months. We estimated the complier average causal effect (CACE) using instrumental variables linear regression estimated via the generalised method of moments, of LP among compliers, defined as participants in the SMC+LP arm who completed all of the LP course.

Prespecified subgroup analyses explored differences in treatment effect according to baseline age (<15 vs 15–17), gender, severity (none vs some school attendance at baseline) and comorbid anxiety (>12 or ≤12 on the HADS anxiety subscale) for the primary outcome, by adding an interaction term to the primary analysis multivariable linear regression model.

Health economic analyses

We conducted a cost-utility analysis of SMC+LP from the health service and public sector perspective. We estimated the incremental net monetary benefit (iNMB) of SMC+LP versus SMC, at a threshold willingness to pay of £20 000 (~US\$30 000) per QALY.³⁴ In the primary analysis, we used the cost of LP charged to the trial (mean £567). In sensitivity analyses we: (1) used the price of LP outside of trial (£620; July 2014 price); and (2) estimated cost of providing the LP intervention within the UK health service (online supplementary table 2). SMC outpatient attendances were extracted from hospital records. Other health-care use was based on parent report. Resource use was combined with 2013 unit costs (online supplementary table 2).^{35–38} In the absence of a paediatric valuation for the EQ-5D-Y, we used the UK adult tariff.³⁹ QALYs were estimated using the area under the curve.⁴⁰ Incremental costs, QALYs and net benefits were



Error bars are 95% Confidence Intervals.

Figure 2 Mean SF-36 physical function over time. LP, Lightning Process; SMC, specialist medical care.

adjusted for baseline values, age, gender and for variables where there was baseline imbalance. Non-parametric bootstrapping methods were used to calculate normally distributed 95% CIs around the iNMB. The probability that SMC+LP is cost-effective at varying willingness-to-pay thresholds was estimated using a cost-effectiveness acceptability curve. Where one item of the EQ-5D-Y was missing ($n=3$), the mean of the other domains (rounded to the nearest integer) replaced the missing value. A high proportion of participants had missing resource use data at 3, 6 and 12 months. Therefore, we conducted two analyses based on the complete case and multiply imputed data sets (online supplementary appendix 2).

All analyses were conducted using Stata (StataCorp. 2013. Stata Statistical Software: Release 13.1. College Station, TX: StataCorp).

RESULTS

Of 657 children assessed in the specialist CFS/ME clinic during the recruitment period, 631 were assessed for study eligibility and 310 were eligible (figure 1). Among those eligible 136 consented to receiving further information and 100 were randomised: 49 to SMC only and 51 to SMC+LP. Fifty-six of these participants were included in the report of whether it was feasible to conduct this randomised controlled trial.²⁴ Recruitment was stopped after the 100th participant was randomised. Eligible children and adolescents who found out more about the trial but were not randomised had lower anxiety and depression scores and attended more school (online supplementary table 3). Participants' mean age was 14 years, 76 were female and all described themselves as British. Participants were disabled by their fatigue: only seven were attending full-time school and 47 described themselves as attending 2 days or less school a week.

Participants' characteristics at baseline were balanced between arms except for pain and anxiety (SCAS) scores (table 1), which was adjusted for in sensitivity analyses. The imbalance in pain and SCAS scores were in opposite directions suggesting that the two arms were not systematically different. Five participants withdrew from the study: two from the SMC and three

from the SMC+LP arm. Outcome data were collected from 92 participants on at least one follow-up occasion. Baseline characteristics were similar between those who did ($n=82$) and did not ($n=18$) provide primary outcome data at 6 months (online supplementary table 4). The mean (SD) time between clinical assessment and primary outcome collection was 6.8 (1.0) and 6.8 (0.7) months in the SMC and SMC+LP arms, respectively. Treatment as allocated was received by 46 (94%) and 39 (76%) participants in the SMC and SMC+LP arms, respectively. Three participants (3/39, 8%) in the SMC+LP arm received the LP course after completing the 6-month follow-up, these participants were included in the analyses.

Mean SF-36 physical function improved more over time in participants allocated to SMC+LP than in those allocated to SMC (figure 2). Participants allocated to SMC+LP had better physical function at 6 months than those allocated to SMC (table 2, adjusted difference in means 12.5 [95% CI 4.5 to 20.5], $p=0.003$). This difference increased to 15.1 (95% CI 5.8 to 24.4, $p=0.002$) at 12 months. These differences were similar when additionally adjusted for baseline anxiety (SCAS) and pain (VAS), when analyses were restricted to participants recruited from February 2011, and with multiple imputation of missing data (table 2). The average between-arm difference in physical function across both 6 and 12 months' follow-up was 14.4 (95% CI 7.3 to 21.5, $p<0.001$). When compliance was taken into account using CACE analyses, the estimated effect of LP at 6 and 12 months was increased compared with the intention to treat (ITT) estimate (table 2). There was little evidence that the effect of LP+SMC compared with SMC on the primary outcome differed according to baseline age, anxiety or school attendance (all interaction $p>0.3$). There was weak evidence (online supplementary table 5) that the effect in males (adjusted difference in means 26.6 [95% CI 8.9 to 44.3]) was greater than that in females (adjusted difference in means 9.0 [95% CI 0.2 to 17.8]) with an interaction p value of 0.08.

Participants in the SMC+LP arm had less fatigue (adjusted difference in means -4.7 [95% CI -7.9 to -1.6], $p=0.003$) (table 3) than those allocated to SMC and a greater improvement

Table 2 Primary outcome

SF-36 physical function	SMC group		SMC+LP group		Crude difference in means (95% CI), P value	Adjusted difference in means* (95% CI), P value	n
	Mean	n	Mean	n			
Baseline	56.0	49	53.0	50			
6 months (primary outcome)†	70.2	37	81.7	45	11.5 (3.1 to 19.8), 0.008	12.5 (4.5 to 20.5), 0.003	81
Children recruited from 1 February 2011	70.5	34	81.4	39	10.9 (1.8 to 20.0), 0.020	11.8 (3.2 to 20.3), 0.008	72
With imputation of missing data	70.9	49	81.1	51	10.2 (2.2 to 18.2), 0.013	11.3 (3.8 to 18.9), 0.004	100
Effect among compliers (CACE)					15.2 (5.0 to 25.3), 0.003	16.6 (6.9 to 26.2), 0.001	81
12 months‡	71.8	38	86.1	42	14.2 (4.6 to 23.8), 0.004	15.1 (5.8 to 24.4), 0.002	79
With imputation of missing data	73.1	49	85.5	51	12.4 (3.3 to 21.5), 0.008	12.6 (4.0 to 21.3), 0.005	100
Effect among compliers (CACE)					16.2 (5.6 to 26.7), 0.003	17.1 (7.0 to 27.3), 0.001	79
Average of 3, 6 and 12-month differences§¶						13.6 (6.7 to 20.4), <0.001	90
Average of 6 and 12-month differences§**						14.4 (7.3 to 21.5), <0.001	87

*Adjusted for age, gender and baseline outcome.
 †Adjusted for age, gender, baseline outcome, baseline Spence Children's Anxiety Scale (SCAS) and visual analogue scale (VAS).
 ‡Higher score=fewer symptoms, better function.
 §Based on a repeated measures analysis that was additionally adjusted for time point as a categorical variable.
 ¶Time as categorical by group interaction, adjusted for age, gender and baseline outcome, p=0.8.
 **Time as categorical by group interaction, adjusted for age, gender and baseline outcome, p=0.7.
 CACE, complier average causal effect; LP, Lightning Process; SMC, specialist medical care.

in anxiety symptoms measured by both the HADS (-3.3 [95% CI -5.6 to -1.0], p=0.005) and the SCAS (-8.7 [95% CI -16.9 to -0.5], p=0.04) scores at 6 months. The difference in means in fatigue score and HADS anxiety score was smaller at 12 months (-3.2 [95% CI -6.3 to -0.1] and -2.8 [95% CI -4.7 to -0.8], respectively). However, the difference in means in SCAS anxiety was greater at 12 months (-12.1 [95% CI -20.1 to -4.1]) and there was evidence that there was less depression among participants allocated to SMC+LP than those allocated to SMC at 12 months (adjusted difference in means in HADS depression score -1.7 [95% CI -3.3 to -0.2], p=0.03). Participants allocated to SMC+LP had better school attendance at 12 months than those allocated to SMC (adjusted difference in means 0.9 days of school per week [95% CI 0.2 to 1.6], p=0.02). Mean pain scores were lower in participants allocated to SMC+LP compared with those allocated to SMC at both 6 and 12 months, but CIs were wide.

Five adverse events were reported (three in the SMC+LP arm). Four were related to participants and one to a parent. None were attributed to either SMC or LP. Physical function at 6 months deteriorated in nine participants, of whom eight were in the SMC arm. Five of the nine had deterioration of ≤10 on the SF-36-PFS (range 0–100) which is less than the minimal clinically important difference (MCID).

EQ-5D-Y questionnaires were completed by 65, 82 and 80 participants at 3, 6 and 12 months, respectively (figure 3); 56 completed EQ-5D-Y at all three follow-up time points. EQ-5D-Y scores were generally higher in the SMC+LP group. Differences in QALYs were evident at 12 months in the multiple imputation data set (table 4, adjusted difference in means 0.095 QALYs [95% CI 0.030 to 0.160], p=0.004), but in the complete case data set the CI included zero (adjusted difference in means 0.080 QALYs [95% CI -0.064 to 0.225], p=0.3).

Complete healthcare use questionnaires were returned by 56 participants at 3 and 6 months and 55 at 12 months, but only 30 participants completed these questionnaires at all three time points. The initial cost of LP was not fully offset by marginally lower costs of other care over the 12-month period. The incremental cost (table 4) of SMC+LP was higher in both complete case (difference in means £445 [95% CI -57 to 947], p=0.08) and multiple imputation data sets (difference in means £390 [95% CI 189 to 591], p<0.005).

Table 4 shows that in the multiple imputation data set there was good evidence that SMC+LP was more cost-effective than SMC alone (iNMB £1508 [95% CI £148 to £2869], p=0.03), although the evidence was much weaker in the complete case data set (figure 4, online supplementary table 6). Sensitivity analyses varying the unit cost of LP treatment made no difference to this conclusion (online supplementary table 7). Sensitivity analyses assuming costs and QALYs are not missing at random⁴⁰ reduced the strength of the evidence that SMC+LP was likely to be cost-effective, but did not alter the conclusion.

DISCUSSION

This is the first randomised trial investigating the effectiveness of the LP for any condition. It is the first trial that has demonstrated the effectiveness of an intervention other than CBT for paediatric CFS/ME. Addition of the LP to SMC improved physical function at 6 months in adolescents with CFS/ME and this difference increased at 12 months. The addition of LP also improved fatigue and anxiety at 6 months and fatigue, anxiety and depression at 12 months. Participants in the LP arm were attending 1 day more of school a week at 12 months on average. The

Table 3 Secondary outcomes

	SMC group		SMC+LP group		Crude difference in means (95% CI), P value	Adjusted difference in means* (95% CI), P value		Adjusted difference in means† (95% CI), P value	
	Mean	n	Mean	n		n	n	n	
Chalder Fatigue score 6 months‡	19.8	37	14.4	44	-5.4 (-8.6 to -2.1), 0.001	-4.7 (-7.9 to -1.6), 0.003	80	-5.4 (-8.9 to -1.9), 0.003	76
Chalder Fatigue score 12 months‡	15.7	38	12.3	42	-3.4 (-6.6 to -0.1), 0.04	-3.2 (-6.3 to -0.1), 0.05	79	-4.0 (-7.2 to -0.7), 0.02	74
Pain VAS 6 months‡	32.8	28	23.4	33	-9.5 (-23.5 to 4.6), 0.2	-11.3 (-23.0 to 0.3), 0.06	58	-9.3 (-21.1 to 2.6), 0.1	58
Pain VAS 12 months‡	32.0	27	21.8	32	-10.2 (-24.6 to 4.2), 0.2	-9.4 (-21.5 to 2.7), 0.1	56	-6.5 (-19.4 to 6.5), 0.3	54
SCAS 6 months‡	37.4	28	24.7	33	-12.7 (-22.0 to -3.3), 0.009	-8.7 (-16.9 to -0.5), 0.04	61	-10.0 (-18.5 to -1.5), 0.02	58
SCAS 12 months‡	36.3	27	19.6	31	-16.7 (-25.9 to -7.5), 0.001	-12.1 (-20.1 to -4.1), 0.004	56	-14.5 (-22.4 to -6.7), <0.001	52
HADS anxiety score 6 months‡	9.7	28	6.1	33	-3.7 (-6.0 to -1.3), 0.003	-3.3 (-5.6 to -1.0), 0.005	60	-3.5 (-5.6 to -1.5), 0.001	57
HADS anxiety score 12 months‡	8.3	27	5.3	33	-3.1 (-5.2 to -0.9), 0.006	-2.8 (-4.7 to -0.8), 0.006	59	-2.6 (-4.7 to -0.4), 0.019	53
HADS depression score 6 months‡	5.9	28	4.2	33	-1.7 (-4.0 to 0.6), 0.1	-1.6 (-3.9 to 0.7), 0.2	59	-1.5 (-3.5 to 0.5), 0.1	57
HADS depression score 12 months‡	4.6	27	2.8	33	-1.9 (-3.6 to -0.2), 0.03	-1.7 (-3.3 to -0.2), 0.03	58	-1.8 (-3.4 to -0.1), 0.04	53
School/college attendance in the previous week 6 months§ (days)	2.6	37	3.2	41	0.7 (-0.1 to 1.4), 0.08	0.7 (0.0 to 1.4), 0.06	77	0.6 (-0.2 to 1.4), 0.1	72
School/college attendance in the previous week 12 months§ (days)	3.1	36	4.1	34	1.0 (0.2 to 1.7), 0.01	0.9 (0.2 to 1.6), 0.02	69	1.0 (0.2 to 1.8), 0.01	65

*Adjusted for age, gender and baseline outcome.

†Adjusted for age, gender, baseline outcome, baseline SCAS and VAS (as appropriate).

‡Higher score=more symptoms, poorer function.

§Higher score=fewer symptoms, better function.

HADS, Hospital Anxiety and Depression Scale; LP, Lightning Process; SCAS, Spence Children's Anxiety Scale; SF-36, 36-item Short-Form health survey; SMC, specialist medical care; VAS, visual analogue scale.

initial cost of LP was not fully offset by lower subsequent costs of healthcare, but the improvements in health-related quality of life meant that SMC+LP is probably cost-effective using a threshold for a QALY of £20 000 (~US\$30 000). Participants in the SMILE trial did not have any serious adverse events attributable to either treatment arm. The majority of those who experienced a deterioration in physical function had a deterioration

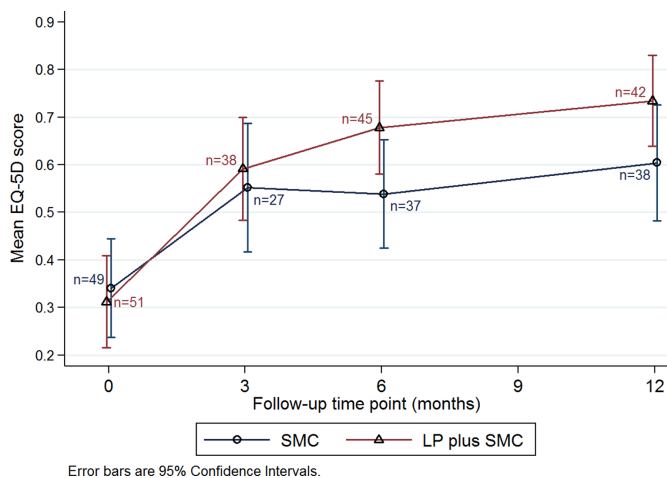


Figure 3 Mean EQ-5D scores, by treatment group. LP, Lightning Process; SMC, specialist medical care.

of ≤ 10 on the SF-36-PFS. The lack of serious adverse events is consistent with other treatment trials in CFS/ME.⁴¹

Strengths of the study include its randomised design and follow-up for 12 months. Participants received SMC that is currently being delivered in the UK Health Service by a multi-disciplinary team, and the LP as it is currently provided. More participants were lost to follow-up in the SMC arm, but baseline characteristics were similar in those followed and not followed up. Complete healthcare use questionnaires were returned by only 55 or 56 participants at each time point. We used multiple imputation to correct for potential bias due to missing data and conducted sensitivity analyses restricted to participants recruited after the protocol changed to collect primary outcome data by telephone, which improved follow-up rates suggesting results were robust. We predefined the clinically important difference (10 points) on the SF-36-PFS and the difference in means was greater than this at both 6 and 12 months. The study was not blinded, so that patient-reported outcomes may have been affected by participants' knowledge of the group to which they were randomised. We did not have capacity to check school attendance using school records, but this could have provided an objective outcome. Further unpublished work suggests this is highly correlated with the self report measure we used. Only 36 (70%) of those allocated LP attended the full course prior to the 6-month follow-up but we estimated the effect in all those who completed the full LP course. The study was originally planned as a feasibility study and although randomised was

Table 4 Analysis of multiple imputation and complete case data of total HC+LP costs and QALYs and NMB (£20 000) at 6 and 12 months; by treatment group, all adjusted for baseline value, age, sex, baseline SCAS and baseline VAS

	SMC			SMC+LP			Incremental difference	
	Mean	(SE)	n	Mean	(SE)	n	(95% CI)	n
Six months complete case								
Total cost (£)	942	(89)	13	1563	(127)	21	621 (323 to 919)	34
QALYs	0.252	(0.021)	22	0.259	(0.016)	32	0.008 (−0.057 to 0.073)	34
NMB at £20 000 per QALY	4225	(578)	13	3762	(461)	21	−464 (−1852 to 925)	34
Six months imputed								
Total cost (£)	1123	(66)	49	1517	(54)	51	394 (236 to 553)	100
QALYs	0.247	(0.015)	49	0.274	(0.014)	51	0.026 (−0.015 to 0.068)	100
NMB at £20 000 per QALY	3819	(328)	49	3954	(276)	51	135 (−733 to 1003)	100
Twelve months complete case								
Total cost (£)	1369	(160)	11	1814	(211)	16	445 (−57 to 947)	27
QALYs	0.551	(0.039)	21	0.597	(0.032)	30	0.080 (−0.064 to 0.225)	27
NMB at £20 000 per QALY	9454	(1202)	11	10615	(1113)	16	1161 (−1966 to 4289)	27
Twelve months imputed								
Total cost (£)	1612	(84)	49	2002	(67)	51	390 (189 to 591)	100
QALYs	0.533	(0.025)	49	0.628	(0.021)	51	0.095 (0.030 to 0.160)	100
NMB at £20 000 per QALY	9042	(521)	49	10551	(427)	51	1508 (148 to 2869)	100

For the complete case results, the n in the final column may not equal the sum of the n in the preceding columns. The n in the preceding columns include participants with complete cost or QALY data, and the n in the final column only includes participants with complete cost and QALY data. HC, health care; LP, Lightning Process; NMB, net monetary benefit; QALY, quality-adjusted life-years; SCAS, Spence Children’s Anxiety Scale; SMC, specialist medical care; VAS, visual analogue scale

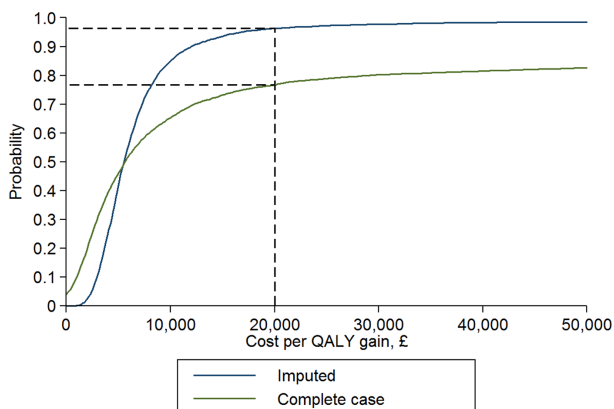
not registered on a trial registry, since the aim was to investigate feasibility rather than effectiveness of the intervention. After establishing feasibility, we applied to register the full trial in June 2012. At this time, the results of our feasibility work suggested we could use either SF-36-PFS or Chalder Fatigue Scale or both which we registered as primary outcomes. We decided to use just the SF-36-PFS and published this in 2013 and in our analyses plan. We did not update the ISTRN site until 2018, however, we uploaded the relevant publications in 2016 and the study website had the updated analyses plan.

The LP may not be suitable for all children and adolescents. Fewer than 30% of eligible children were randomised. We do not know why the majority did not want to take part in the trial

but it may be because they did not want to take part in groups or travel for 3 consecutive days. We felt it would be unethical to have a control group without treatment and therefore we only know that LP is effective in addition to SMC and not whether it is effective on its own. We only recruited children aged 12 and over who were not housebound and who spoke English. We do not know whether LP is effective, acceptable or feasible for those who are severely affected, less than 12 years old, or do not speak English. The study was registered after demonstrating feasibility. The analysis includes participants who were recruited prior to registration of the study. This does not comply with ICMJE and BMJ guidance on trial registration. The reasons for this have been explained in the paper.

Participants in both treatment arms improved. Those receiving SMC alone had a mean improvement that was similar to that seen in adults receiving CBT or GET.⁴¹ The improvement in SF-36-PFS in those receiving SMC+LP is consistent with those receiving treatment in previous paediatric trials investigating both family-based and individual CBT.^{17 20} We predefined the MCID as 10 points on the SF-36-PFS based on consensus statements. Subsequent work by our team has shown that this is a clinically significant change in physical function for children with CFS/ME.⁴² Ten points equates to a minimum of two step changes on the SF-36-PFS. This can be either one-step change on two questions, or two-step changes on one question. The SF-36 asks: ‘Does your health limit you in these activities? If so, how much?’ As an example, one-step change could be: ‘Yes, limited a lot’ to ‘Yes, limited a little’ or ‘Yes, limited a little’ to ‘No, not limited at all’ to different questions such as ‘climbing several flights of stairs’ or ‘walking 100 yards’ or ‘walking half a mile’. The participants in our study who received SMC only did not improve as much as other trials investigating CBT^{17 20} which may be because on average they had less than half the number of treatment sessions.

Participants in the SMC+LP arm maintained or increased improvements compared with SMC alone at 12 months and



* For any selected willingness to pay for a QALY (x axis), the probability that SMC plus LP is cost-effective can be estimated by reading up from that point on the x axis to the curve and then reading across to the probability (y axis). The dashed lines represent the lower NICE threshold of £20,000 per QALY gained.

Figure 4 Cost-effectiveness acceptability curves* based on complete case and multiply imputed estimates of incremental costs and QALYs of SMC plus LP at 12 months. LP, Lightning Process; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-years; SMC, specialist medical care.

this was true for both the ITT and the CACE analyses. This is in contrast to previous trials investigating internet-based CBT where the treatment effects were sustained but the difference between the two trial arms was reduced at 12 months compared with 3 months,^{19,22} and family-focused CBT versus psychoeducation where treatment differences at 3 months were not maintained at 6 or 12 months.²⁰

There is only one study²³ investigating LP which used qualitative interviews to explore the views of nine 14–26 year-olds about their experiences. The main difference between LP and CBT appears to be the emphasis placed on physiological responses and causal attributions²³ but we do not know whether these explain the greater effectiveness of LP. We do not know which aspects of the LP are the most important or helpful. Some young people who received LP value the theory, others the practical sessions or the homework.²³ Further research is needed to understand why LP improves outcomes at 6 and 12 months and which aspects of the LP contribute to its effectiveness.

CONCLUSIONS

The addition of the LP to SMC may be helpful to children with CFS/ME. However, this study needs to be replicated before the LP should be offered in the NHS.

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Contributors EMC obtained the funding, and designed and supervised the trial. DMG conducted the statistical analysis and compiled the results tables. KG conducted the health economic analyses and compiled the health economic tables. WH contributed to the study design and supervised the health economic analyses. JACS and AAM contributed to the study design and cosupervised the statistical analyses. LB contributed to the study design and running the trial. SMC managed the data and contributed to the statistical analyses. NM contributed to the study design. All authors contributed to the data interpretation and writing the paper. EMC is the guarantor. The authors had access to all the data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Disclaimer No member of the LP team had any involvement in the analyses or in writing the paper. No member of the Linbury Trust or the Ashden Trust had any involvement in the design, analyses or in writing the paper. This report is an independent research and the views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. The funders and the sponsor of the study had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication. All researchers involved in this study were independent from both the funders and the sponsor.

Competing interests Financial support for the submitted work was received from the Linbury Trust and the Ashden Trust. EMC and SMC have received fellowship grants from the NIHR. JACS has received grants from the NIHR. EMC runs the specialist CFS/ME service at Royal United Hospital NHS Foundation Trust, has received one grant from MRC, one grant from the NIHR and is a medical advisor to the Sussex and Kent ME/CFS Society. The authors declare they did not receive any funding from the Lightning Process.

Ethics approval A favourable ethical opinion was given on 8 September 2010 (reference 10/H0206/32) by South West 2 Local Research Ethics Committee. Two favourable opinions were provided for amendments to study documents and protocol on 31 May 2011 and 6 September 2012.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Given the nature of this data set, access is controlled. Requests are referred to the University of Bristol Data Access Committee (DAC) for approval before data can be released under an appropriate data access agreement. For details on how to access data please see the repository record at <http://dx.doi.org/10.5523/bris.1myzti8qnv48g2sxtx6h5nice7>.

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Notice of correction and clarification: Clinical and cost-effectiveness of the Lightning Process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial

NOTICE OF CORRECTION AND CLARIFICATION

This article (*Archives of Disease in Childhood* 2018;103:155–164; DOI: 10.1136/archdischild-2017-313375) has been corrected and republished. The previous text of the article, marked up to show all the changes made, has been posted as an online supplementary file to the republished article.

The changes are extensive but clarificatory and for this reason the editors have issued a correction and not a retraction. A linked Editor's note provides more background to this decision (10.1136/archdischild-2017-313375ednote).

The corrections include, but are not limited to, the following. (All corrections are shown on the online marked version, which is free to access.) Some changes to punctuation and reference numbers have not been noted below but are included in the marked copy.

ABSTRACT

'SF-36-PFS at three and 12 months' was added to the list of secondary outcomes in the 'Main outcome measures' section. In the Results section 'We recruited 100 participants, of whom 51 were randomised to SMC+LP.' has been changed to 'We recruited 100 participants between September 2010 and September 2013. We tested the feasibility of running the trial with a feasibility phase (29th September 2010 to 18th September 2012). The full trial was registered in June 2012 when we had determined it was a feasible study. Of the 100 participants, 51 were randomised to SMC+LP.' In the Results section, 'probably' has been deleted and the p value changed to 0.03 in the following line: 'SMC+LP was probably more cost effective in the multiple imputation dataset (difference in means in net monetary benefit at 12 months £1474, [95% CI £111 to £2836], $p=0.034$) but not for complete cases.'

INTRODUCTION

Paragraph 1: 'affects' changed to 'effects'. Paragraph 3: 'LP is not available in the NHS.' has been deleted.

Methods, Study design and participants

'Between September 2010 and April 2013, we recruited participants after clinical assessment by the Bath/Bristol paediatric CFS/ME service, a large regional and national NHS specialist service.' has been changed to read 'Between September 2010 and September 2013 we recruited participants after clinical assessment by the Bath/Bristol paediatric CFS/ME service, a large regional and national NHS specialist service. We tested the feasibility of running this trial with a feasibility phase (29th September 2010 to 18th September 2012). We determined the trial was feasible in June 2012 and registered the full trial (31st July 2012). We applied for an amendment to recruit children into the full trial as opposed to a feasibility trial (see web table 1 for detailed description of amendments). Full trial first randomisation was the 19th September 2012. We continued seamlessly with participant recruitment without any interim between-group comparison of participant outcome data from the feasibility phase. Children from both phases (feasibility and full) were analysed.'

Methods, Randomisation and masking

'the randomised intervention was conveyed during the recruitment interview' has been changed to 'the randomised intervention was conveyed after obtaining consent, during the recruitment interview'.

Methods, Interventions

'Sessions were delivered by a range of trained and supervised professionals including doctors...' has been changed to read 'Sessions were delivered by a range of professionals including doctors...'

The following paragraph was removed: 'Lightning Process practitioners have completed a Diploma through the Phil Parker Training Institute in Neurolinguistic Programming, Life Coaching and Clinical Hypnotherapy. This diploma is examined through written and practical exams and is accredited by the British Institute of Hypnotherapy and NLP. Following the Diploma, Lightning Process practitioners undertake a further course to learn the tools and delivery required for the Lightning Process after which they must pass both a practical and written exam. Practitioners undertake supervision and CPD in order to further develop their skills and knowledge. They are regulated by the Register of Lightning Process practitioners, adhere to a Code of Conduct, and there is a Professional Conduct Committee that oversees complaints and professional practice issues.'

Methods, Outcomes

The first paragraph as published read:

'The primary outcome was the the 36-Item Short-Form Health Survey Physical Function Subscale (SF-36-PFS)²⁶ analysed as a continuous variable collected at 6 month post-randomisation. Secondary outcomes were the SF-36-PFS at 3 and 12 months, and school attendance (days per week), the Chalder Fatigue Scale²⁷ and quality-adjusted life years (QALYs, derived from the EQ-5D-Y)²⁸ at 3, 6 and 12 months. Pain was measured by a Visual Analogue Scale (VAS) at 6 months. All were self-completed by participants. Participants also completed the Hospital Anxiety and Depression Scale (HADS)²⁹ and the Spence Children's Anxiety Scale (SCAS)³⁰ at assessment, and at 3, 6 and 12 months. At 3, 6 and 12 months, parents completed an adapted four-item Work Productivity and Activity Impairment: General Health V2.0 questionnaire (V2.0)³¹ and a resource use questionnaire assessing their child's health service use (eg, general practitioner or specialist care), educational service use (eg, school counsellor), health-related travel and other family costs.'

This has been expanded to read as follows:

'The primary outcome was the SF-36 physical function subscale (SF-36-PFS²⁶) analysed as a continuous variable collected at 6 months post-randomisation. We chose the SF-36 based on qualitative work conducted in the feasibility phase of the study.²⁴ We have reported that parents and participants 'commented that the school attendance primary outcome did not accurately reflect what they were able to do, particularly if they were recruited during, or had transitioned to, A levels during the study'. In addition, 'we were aware of some participants who had chosen not to increase school attendance despite increased activity.' We therefore concluded that: "trials involving 17 and 18 year olds should consider alternative primary outcome measures to school attendance as it is difficult to assess for those transitioning from GCSEs to A levels, and may not be appropriate for those who do not consider school attendance their primary goal". At this stage, our recommendation was that a "full study uses other primary outcomes, such as the SF-36 or the Chalder Fatigue Scale and uses school attendance as a secondary outcome.' These findings informed our application for our ethical amendment to a full study in 2011 (see web table 1). And were published in our feasibility paper in 2013.²⁴

Qualitative interviews with SMILE participants then formed part of a larger study which described the conceptual model for paediatric CFS/ME.²⁷ In this study, physical activity (or disability) is described by children as being pivotal because of the impacts on social participation and emotional well-being. While school was deemed to be an important contextual factor, these qualitative results led us to choose the SF-36-PFS as a primary outcome with school attendance as a secondary outcome. There was no analysis of any outcome data during or after the feasibility phase until the entire trial was completed.

Secondary outcomes were the SF-36-PFS at three and 12 months, and school attendance (days per week), the Chalder Fatigue scale²⁸, pain (visual analogue scale), Hospital Anxiety and Depression Scale (HADS)²⁹, Spence Children's Anxiety Scale (SCAS)³⁰ and quality-adjusted life years (QALYs, derived from the EQ-5D-Y)³¹ at three, six and 12 months. At three, six and 12 months parents completed an adapted four item Work Productivity and Activity Impairment: General Health V2.0 (WPAI:GH) questionnaire (V2.0)³² and a resource use questionnaire assessing their child's health service use (eg, GP or specialist care), educational service use (eg, school counsellor), health related travel and other family costs.'

Methods, Sample size

This paragraph originally read:

‘We used a consensus definition for a small clinically important difference of 10 points on the SF-36-PFS.³² Thirty two to 50 participants in each arm are required to detect a between-group difference of 8 to 10 points on the SF-36-PFS (SD 10) at 6 months with 90% power and 1% two-sided significance. Allowing for 10% to 20% non-collection of primary outcome data, we aimed to recruit 80 to 112 participants.’

It has been changed to read:

‘A consensus definition for a small clinically important difference on the SF-36-PFS at 6 months follow-up is 10 points.³³ However, we did not want to miss a smaller but still potentially important effect of as low as eight points. To detect a between-group difference of 8 to 10 points with 90% power, 1% two-sided significance and SD of 10 requires between 32 and 50 participants per group for analysis. Allowing for 10% to 20% non-collection of primary outcome data, we aimed to recruit between 80 ($32 \times 2/0.8$) and 112 ($50 \times 2/0.9$) participants.’

Methods, statistical analysis

First paragraph: ‘Sensitivity analyses of the primary outcome adjusted for variables for which there was baseline imbalance; excluded those recruited up to 31 January 2011 preceding the protocol amendment; and used multiple imputation of missing data (see online supplementary appendix 1 for details).’ now reads ‘Sensitivity analyses of the primary outcome adjusted for variables for which there was baseline imbalance; excluded those recruited up to 31 January 2011 preceding the protocol amendment to allow collection of follow-up data by phone; and used multiple imputation of missing data.’ The line ‘Twelve-month outcome data were analysed similarly.’ has been deleted. The line ‘We did not analyse 3 month outcomes except in this repeated measures analysis for SF-36-PFS as these were unlikely to be informative since the primary follow-up was at 6 months.’ has been added.

Methods, Health economic analyses

Some references have been renumbered, as have some references to online supplementary material. The penultimate paragraph has had a further reference to online supplementary material added.

RESULTS

First paragraph: the text ‘56 of these participants were included in the report of whether it was feasible to conduct this RCT.²⁴’ was added before ‘Recruitment was stopped after the 100th participant was randomised.’

Second paragraph: the sentence ‘The imbalance in pain and SCAS scores were in opposite directions suggesting that the two arms were not systematically different.’ was added. Some online supplementary tables were renumbered. ‘Three participants in the SMC+LP arm received the LP course after completing the 6 month follow-up.’ was replaced by ‘Three participants (3/39, 8%) in the SMC+LP arm received the LP course after completing the 6 month follow-up, these participants were included in the analyses.’

Third paragraph: ‘The average between-arm difference in physical function across both 6 and 12 month follow-up was 14.4 (95% CI 7.3 to 21.5), $p < 0.001$. The estimated effect of LP (using CACE analyses) among compliers at 6 and 12 months was increased compared with the intention-to-treat (ITT) estimate (table 2).’ was replaced by ‘The average between-arm difference in physical function across both 6 and 12 month follow-up was 14.4 (95% CI 7.3, 21.5, $p < 0.001$). When compliance was taken into account using CACE analyses, the estimated effect of LP 6 and 12 months was increased compared with the ITT estimate (table 2).’

Fourth paragraph, first sentence: ‘ $p = 0.039$ ’ was replaced by ‘ $p = 0.04$ ’; second sentence: the word ‘somewhat’ has been deleted from ‘The difference in means in fatigue score and HADS anxiety score were somewhat smaller at 12 months’; third sentence: ‘ $p = 0.030$ ’ replaced by ‘ $p = 0.03$ ’; fourth sentence: ‘ $p = 0.18$ ’ replaced by ‘ $p = 0.2$ ’; fifth sentence: ‘Pain scores were lower’ replaced by ‘Mean pain scores were lower’.

Sixth paragraph: ‘ $p = 0.276$ ’ replaced by ‘ $p = 0.03$ ’.

Seventh paragraph: ‘Complete healthcare use questionnaires were returned by between 55 (55% at 12 months) and 56 (56% at 3 and 6 months) participants, but only 30 (30%) completed these questionnaires at all three time points (see online supplementary table S5 for details).’ changed to ‘Complete healthcare use questionnaires were returned by 56 participants at 3 and 6 months and 55 at 12 months, but only 30 participants completed these questionnaires at all three time points.’ In the final sentence the p values 0.082 and 0.000 have been replaced by 0.08 and < 0.005 respectively.

Eighth paragraph: p value 0.034 has been changed to 0.03; references to online supplementary material have been added; the sentence ‘Sensitivity analyses assuming costs and QALYs are not missing at random⁴⁰ did not alter the conclusion that SMC+LP was likely to

be cost-effective, but reduced the strength of the evidence.’ now reads ‘Sensitivity analyses assuming costs and QALYs are not missing at random⁴⁰ reduced the strength of the evidence that SMC+LP was likely to be cost-effective, but did not alter the conclusion.’

DISCUSSION

Paragraph one has been amended from ‘Participants in the LP arm were attending 1 day more of school a week at 12 months’ to read ‘Participants in the LP arm were attending 1 day more of school a week at 12 months on average.’ Reference 40 was changed to 41.

Paragraph two: ‘that we followed patients’ was changed to ‘follow’. The following sentence was added: ‘We did not have capacity to check school attendance using school records, but this could have provided an objective outcome. Further unpublished work suggests this is highly correlated with the self report measure we used.’ The following was added to the end of paragraph two: ‘The study was originally planned as a feasibility study and although randomised, was not registered on a trial registry, since the aim was to investigate feasibility rather than effectiveness of the intervention. After establishing feasibility, we applied to register the full trial in June 2012. At this time, the results of our feasibility work suggested we could use either SF-36-PFS or Chalder Fatigue scale or both which we registered as primary outcomes. We decided to use just the SF-36-PFS and published this in 2013 and in our analyses plan. We did not update the ISRCTN site until 2018, however, we uploaded the relevant publications in 2016 and the study website had the updated analyses plan.’

Additional sentences were added to the end of paragraph three: ‘The study was registered after demonstrating feasibility. The analysis includes participants who were recruited prior to registration of the study. This does not comply with ICMJE and BMJ guidance on trial registration. The reasons for this have been explained in the paper.’

The following section was added to paragraph four:

‘We pre-defined the minimally clinically important difference as 10 points on the SF-36-PFS based on consensus statements. Subsequent work by our team has shown that this is a clinically significant change in physical function for children with CFS/ME.⁴² Ten points equates to a minimum of two step changes on the SF-36-PFS. This can be either one step change on two questions, or two step changes on one question. The SF-36 asks: ‘Does your health limit you in these activities? If so, how much? As an example, one step change could be: ‘Yes, limited a lot’ to ‘Yes, limited a little’ or ‘Yes, limited a little’ to ‘No, not limited at all’ to different questions such as ‘climbing several flights of stairs’ or ‘walking 100 yards’ or ‘walking half a mile’.’

The last line of the paragraph (‘As we did not compare LP with either a full course of only CBT or GET we do not know if LP is more or less effective than either of these treatment approaches.’) was deleted.

A new section, ‘Conclusions’, was added.

ACKNOWLEDGEMENTS

The statement ‘No member of the LP team had any involvement in the analyses or in writing the paper.’ has been moved to the Disclaimer section.

CONTRIBUTORS

The lines ‘The authors had access to all the data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.’ have been moved from the Data sharing statement to the Contributors section.

DISCLAIMER

The following lines were added to the Disclaimer: ‘The funders and the sponsor of the study had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication. All researchers involved in this study were independent from both the funders and the sponsor.’

COMPETING INTERESTS

This section has been expanded to read as follows: ‘Financial support for the submitted work was received from the Linbury Trust and the Ashden Trust. EMC and SMC have received fellowship grants from the NIHR. JACS has received grants from the NIHR. EMC runs the specialist CFS/ME service at Royal United Hospital NHS Foundation Trust, has received one grant from MRC, one grant from the NIHR and is a medical advisor to the Sussex and Kent ME/CFS Society. The authors declare they did not receive any funding from the Lightning Process.’

ETHICS APPROVAL

This section has been expanded to read as follows: 'A favourable ethical opinion was given on 8 September 2010 (reference 10/H0206/32) by South West 2 Local Research Ethics Committee. Two favourable opinions were provided for amendments to study documents and protocol on 31 May 2011 and 6 September 2012.'

TABLES

Changes have also been made to tables 1–4; these are shown in the marked copy and relate to rounding up some entries and adding information to the legends.

REFERENCES

A new reference 27 has been added (Parslow *et al*). The previous reference 28 (Ravens-Sieberer *et al*) is now reference 31. Subsequent references have been renumbered. A new reference (Brigden *et al*) has been added.

COMPETING INTERESTS

Additional sentence: 'The authors declare they did not receive any funding from the Lightning process.'



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Editor's note on correction to Crawley et al. (2018)

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Crawley EM, Gaunt DM, Garfield K, et al. Clinical and cost-effectiveness of the Lightning Process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial. *Arch Dis Child* 2018;103:155–64. doi: 10.1136/archdischild-2017-313375.

This trial (ISRCTN81456207: registration July 31st 2012) was originally submitted to *Archives of Disease in Childhood (ADC)* in May 2017 and underwent external peer review. It was accepted after one revision on July 28th 2017, was published online first on September 20th 2017 and in print in the February 2018 edition (Volume 103, issue 2).

The study tested the effectiveness of the Lightning Process, a neurolinguistic programming intervention used widely but never formally tested, in children and young people with chronic fatigue syndrome (CFS) recruited between 2010 and 2013. Though the number of participants was small and the enrolment rate low, analysis suggested a benefit in terms of physical function (measured by the standard SF 36 scale) at both 6 and 12 months after intervention. Secondary analysis indicated that the treatment was likely to be cost effective.

In January 2018, *ADC* was contacted by a group of readers (<http://www.virology.ws/2018/01/30/trial-by-error-a-letter-to-archives-of-disease-in-childhood/>) with specific criticisms of the paper. The authors were criticised for a lack of clarity with respect to International Committee of Medical Journal Editors (ICMJE) and BMJ policies on trial registration (in place since 2007) and for not fully adhering to CONSORT guidance on trial reporting.^{1,2} The journal was criticised for not detecting these issues during the review process.

The issues related to the following areas:

1. The inclusion of children from the feasibility phase (recruited between October 2010 and July 2012) in the analysis of the main trial. The authors sought approval for the change from the relevant ethics committee (June 2012), but, the chronology was not clear in the original paper. In part this was because no timeline was provided and in part because the tense used in the text implied that recruitment had been purely prospective. The ISRCTN entry (dated July 2012) stated: 'the study started as a feasibility study in October 2010'. In the text, for example the authors stated that 'young people and parents will be asked to read the information' and that 'we have now shown that it is possible to run the study and are planning to convert the study to a randomised trial' suggesting that recruitment of eligible participants had not started in June 2012. The editorial and review processes did not pick up these issues with the timeline at this stage.
2. A concern that the primary outcomes were "swapped" between the feasibility and full trials. The authors' feasibility study publication explains why the 36-Item Short-Form Health Survey Physical Function Subscale (SF-36-PFS) was selected as the primary outcome for the full trial, after school attendance had been considered as a potential primary outcome in the feasibility study, but this was not explained in the article. The SF-36-PFS was also included as the primary outcome in the published protocol for the full trial.

When these criticisms were raised with the journal, we acknowledged them as valid and embarked on a lengthy clarification process with the authors. To do so with the appropriate rigour has taken over a year and the chronology is worth detailing.

1. January 2018: Criticisms of the paper received
2. February 2018: An external review of the chronology to establish the validity of the criticisms and confirmation that substantial clarification of the above issues would be needed
3. March 2018: Feedback of detailed comments to the authors with instructions as to the prerequisites for the clarified paper
4. June 2018: The posting of an e-letter linked to the paper alluding to steps being taken to address the criticisms (<https://adc.bmj.com/content/103/2/155.responses>)
5. July 2018: First version of the corrected paper received. Sent for statistical review and review by an experienced *ADC* editor not involved with handling the article previously
6. July 2018: Reviewers' and editors' comments sent to authors

7. October 2018: First revision of the paper received. Sent for re-review by previous reviewers
8. November 2018: Reviewers' and editors' comments sent to authors
9. November 2018: Second revision received and, after further discussion and editorial review, provisionally accepted in February 2019
10. March 2019: Formal acceptance of revised paper.

The final version includes acknowledgement from the authors that the study was not fully ICMJE compliant. The process has additionally involved seeking assurance from the authors that the change in primary outcome was not influenced by (positive) findings in the feasibility phase.

We are now satisfied that the paper is a robust account of events and that it can be considered as a contribution to the field of CFS research.

We agree with the correspondents that the article as originally published lacked sufficient detail and clarity for readers to fully understand the study as conducted. Therefore we have published a substantial correction³ which adds extensive clarifications to the study's timeline and methods.

We have taken the step of republishing the article with the clarifications incorporated because they are so extensive. This republished article links to a detailed note of correction and clarification and we have also posted a breakdown of every change to the article, to ensure transparency (10.1136/archdischild-2017-313375corr1 and 10.1136/archdischild-2017-313375).

BMJ policy requires prospective registration of randomised trials but we do not consider a failure to enforce that policy grounds for retraction. The corrections to the article are mainly clarifications and we do not believe the article meets any of the Committee on Publication Ethics' criteria for retraction.

In addition, we have revised our processes in relation to EQUATOR-CONSORT guidance to ensure robustness. As is clear on our instructions to authors, no trial in which recruitment predates trial registration will be considered further.

We are satisfied that the correction this manuscript has undergone has addressed the criticisms raised and we are grateful to the correspondents for bringing them to our attention.



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- 1 <http://www.icmje.org/> [Accessed 27 Jan 2019].
- 2 <http://www.equator-network.org/reporting-guidelines/consort/> [Accessed 27 Jan 2019].
- 3 Crawley EM, Gaunt DM, Garfield K, *et al*. Clinical and cost-effectiveness of the Lightning Process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial. *Arch Dis Child* 2018;103:155–64.