

## Randomised Feasibility Study of Physiotherapy for Patients with Functional Motor Symptoms

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**ABSTRACT**

**Objective:** To determine the feasibility of conducting a randomised controlled trial of a specialist physiotherapy intervention for functional motor symptoms (FMS).

**Methods:** A randomised feasibility study was conducted recruiting patients with a clinically established diagnosis of FMS from a tertiary neurology clinic in London, UK. Participants were randomised to the intervention or a treatment as usual control. Measures of feasibility and clinical outcome were collected and assessed at 6 months.

**Results:** Sixty individuals were recruited over a nine month period. Three withdrew, leaving 29 intervention and 28 controls participants in the final analysis. Thirty-two per cent of patients with FMS met the inclusion criteria, of which 90% enrolled. Acceptability of the intervention was high and there were no adverse events. At six months, 72% of the intervention group rated their symptoms as improved, compared to 18% in the control group. There was a moderate to large treatment effect across a range of outcomes, including three of eight SF36 domains ( $d=0.46-0.79$ ). The SF36 Physical Function was found to be a suitable primary outcome measure for a future trial; adjusted mean difference 19.8 (95% CI 10.2–29.5). The additional quality adjusted life years (QALY) with intervention was 0.08 (95% CI 0.03–0.13), the mean incremental cost per QALY gained was £12,087.

**Conclusions:** This feasibility study demonstrated high rates of recruitment, retention, and acceptability. Clinical effect size was moderate to large with high probability of being cost effective. A randomised controlled trial is needed.

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## **INTRODUCTION**

Functional neurological disorder (conversion disorder), accounts for 15% of all new patients seen in general neurology clinics.[1,2] Approximately 10-50% present with functional motor symptoms (FMS), typically weakness, tremor and gait disorder.[1,2] These patients experience disability and distress equivalent to those suffering from degenerative neurological disease.[3] Prognosis is poor; at an average of seven years follow up, 40% have similar or more severe symptoms, and the majority remain symptomatic.[4]

Despite the prevalence and impact of symptoms, there is limited evidence regarding effective treatment. Psychological therapy is traditionally proposed as the treatment modality of choice, but physically based interventions have emerged as a promising treatment. A randomised delayed-start study of three weeks inpatient physical rehabilitation “with a cognitive behavioural framework”, found an improvement in measures of physical functioning which were maintained at 12 months follow up.[5] A systematic review of physiotherapy for FMS (including 564 subjects) supports the view that physiotherapy outcomes are promising and warrant further investigation with a randomised controlled trial (RCT).[6] The interventions employed in this literature differ from physiotherapy for typical neurological disease which we have described in consensus recommendations for physiotherapy practice.[7] This approach has been tested in two cohort studies which report improvement in physical functioning.[8,9]

We aimed to determine the feasibility of an RCT of specialist physiotherapy for FMS. Specific aims were to test acceptability and feasibility of a treatment protocol based on consensus recommendations; to test the utility of a range of outcome measures; and to collect outcome data to determine the sample size required for a large scale trial.

## **METHODS**

### **Study Design and Setting**

We conducted a two parallel arm, randomised feasibility study of a five day specialist physiotherapy-led intervention versus a treatment as usual control for patients with FMS. This study took place at the National Hospital for Neurology and Neurosurgery, London, UK.

Approval was obtained from the National Research Ethics Service Committee London – City Road & Hampstead (14/LO/0572). All participants gave written informed consent. A trial steering committee oversaw the conduct of the trial. The trial was registered at ClinicalTrials.gov (NCT02275000).

## **Participants**

Sixty participants were recruited from new patients attending an outpatient neurology clinic specialising in movement disorders and FMS. Inclusion criteria were: a clinically established diagnosis of FMS according to Fahn-Williams criteria;<sup>[10]</sup> age 18 years or older; completed diagnostic investigations; acceptance of the diagnosis on the balance of probability (i.e. we did not exclude patients who continued to express some doubt over the diagnosis); FMS duration of at least six months; symptoms severe enough to cause distress or impairment in social or occupational functioning. Exclusion criteria were: unable to understand English; pain or fatigue that we judged to be the primary cause of the patient's disability; prominent dissociative seizures for which the patient required assistance to manage; clinically evident anxiety or depression that we felt required assessment before starting physiotherapy treatment; high level of disability that prevented participation in an outpatient/day hospital environment; and unable to attend five consecutive days of treatment.

Prior to enrolment, all participants attended a consultation with the study neurologist (MJE) where the diagnosis of FMS was made. Each patient received a standard comprehensive explanation of the diagnosis.<sup>[11]</sup> The patient was also referred to online sources of information ([www.neurosymptoms.org](http://www.neurosymptoms.org), [www.FNDHope.org](http://www.FNDHope.org)). Patients meeting the selection criteria were provided with written information about the trial and invited to return for consent and baseline assessment.

## **Randomisation and masking**

Eligible consenting participants were randomly allocated (1:1) to the intervention or control group using a secure online randomisation application (Sealed Envelope, London, UK). The randomisation procedure was completed after baseline assessment by the study lead physiotherapist (GN) or independent research physiotherapist (MD). Participants were

immediately informed of their treatment allocation. Both participants and clinicians were unmasked to treatment allocation.

## **Procedures**

The intervention was a protocolised five day programme, delivered by a neurophysiotherapist (KH) who had undertaken additional specific training (from GN). Participants were admitted to a day hospital for five consecutive days, within four weeks of baseline assessment. The first session was a joint consultation with the neurologist and physiotherapist where diagnostic information was reviewed and the aims of the programme discussed. These were explained as retaining movement and learning how to manage symptoms in the longer term. The programme consisted of eight sessions over five consecutive days, each lasting 45-90 minutes. Each session included education, movement retraining, and development of a management plan. Education was centred on a physical biased aetiological model for functional motor symptoms.[8] The physiotherapist and participant collaboratively devised a symptom formulation taking into account triggering events, comorbidity, psychological factors, self-focussed attention, and unhelpful reinforcement of symptomatic movement patterns. Movement retraining aimed to restore normal movement during problematic activities by redirecting the focus of motor attention.[7] The participant and physiotherapist made notes in a workbook, documenting the individualised symptom formulation, information about FMS, specific symptom management strategies, daily reflections, a personal self management plan and what to do in case of symptom exacerbation.

For controls, a referral was made to the participant's local neurophysiotherapy service. The referral letter contained information about the diagnosis, specific treatment goals, and welcomed contact for further information regarding the diagnosis or treatment advice. No attempt was made to standardise treatment provided. Input received was recorded, based on patient report.

Participants were re-assessed at four weeks and six months by MD. For the intervention group, the four week assessment coincided with the final day of treatment.

## Outcome Measures

Measures of feasibility were: recruitment rate; retention; intervention fidelity; and acceptability of the intervention. Safety was assessed by participant reported adverse events. We did not specify a primary clinical outcome measure as the primary aim of this study related to feasibility. Clinical outcome measures collected were: Short Form 36 (SF36);[12] Hospital Anxiety and Depression Scale (HADS);[13] EQ-5D-5L;[14] Work and Social Adjustment Scale (WSAS);[15] 5-point patient rated Clinical Global Impression Scale (CGI);[16,17] Disabilities of the Arm Shoulder and Hand (DASH);[18] Functional Mobility Scale;[19] Berg Balance Scale;[20] Brief Illness Perception Questionnaire (B-IPQ);[21] and 10 metre timed walk. The CGI was collapsed into two groups: good outcome (ratings of much improved and improved) and poor outcome (ratings of no change, worse or much worse). We collected additional data on the economic impact of symptoms as well as qualitative data related to the intervention, which will be reported elsewhere. Participants in the intervention group completed a feedback form to assess acceptability of the intervention.

## Statistical Analysis

A power calculation was not performed as the primary aim of this study was to assess feasibility. The sample size of 60 was predetermined and considered sufficient to meet the objectives of collecting data on outcome measure variation, recruitment and retention. For continuous measures, the difference between groups was assessed using a linear regression model, adjusting for the baseline scores of the measure. Treatment effect was calculated using Cohen's *d* to allow comparisons between outcome measures.[22] Incomplete cases due to drop out were excluded from analysis. Data were analysed using SPSS version 22. The EQ-5D-5L utility scores[23] were converted to Quality Adjusted Life Years (QALYs) by calculating the area under the curve adjusting for baseline differences.[24] Physiotherapist and neurologist salaries, on-costs and overheads were obtained from the Personal Social Services Research Unit[25] and multiplied by the average contact time per patient. Other costs were obtained from trial costings documentation and were for the 2014/2015 financial year. The estimated mean cost per patient of the intervention minus the mean cost of control neurophysiotherapy services was divided by the difference in QALYs gained between groups to calculate the incremental cost-effectiveness ratio (ICER).

## RESULTS

The trial profile is shown in figure 1. Between Sept 8 2014, and Jun 4 2015, 210 new patients were screened and 143 excluded. The commonest reasons for exclusion were dominant pain (n=57, 27% of screened patients), clinically evident anxiety or depression requiring assessment (n=50, 24% of screened patients) and dominant fatigue (n=22, 10% of screened patients). Seven patients declined to participate and the remaining 60 were recruited and randomly assigned to the intervention (n=30) and control (n=30) groups. 31.9% (95% CI 25.6–38.2) of screened patients met selection criteria. Ninety of eligible patients consented to participate. The number assessed at the primary endpoint was 29 for the intervention group and 28 for the control group. The dropout rate was 5%. One participant from the intervention group was unable to attend the final assessment but they agreed to complete questionnaires by post; their final physical assessment measures (Berg Balance Scale and 10 metre walk time) were therefore missing. Three participants from the control group did not attend the interim four week assessment.

Baseline characteristics of the participants are shown in table 1. The mean age was 43 years, 72% were women and approximately half the participants were not working due to ill health. Mean FMS duration was 5.8 years (SD 7.3) and mean age of symptom onset was 37 (SD 12.0).

Continuous clinical outcome measures for baseline and six month outcome are reported in table 2, (see supplementary online data for four week outcome scores). Inspection of baseline data suggested that the control group had generally worse scores than the intervention group, which were accounted for in the analysis.

We tested the assumptions of the regression model, which were met. After adjusting for baseline scores, at six months the intervention group had superior scores (representing better health) in three domains of the SF36 (Physical Function, Physical Role, and Social Function); the Berg Balance Scale, the 10 metre walk time, the Functional Mobility Scale, the DASH, and the composite B-IPQ score. Two outliers skewed the results of the 10 metre walk time, inflating the treatment effect. After removing outliers, the mean difference remained significant. Effect sizes were medium to large, ranging from  $d=0.46$  to 0.79. Outcomes that

were not different between groups were the remaining five domains of the SF36, HADS anxiety and depression scores, and the WSAS.

The CGI data are presented in table 3. At six months 72% of the intervention group reported a good outcome, compared to 18% in the control group. Thirty-two per cent of the control group felt that their symptoms had got worse from baseline to six month follow up, compared to 3% in the intervention group.

The mean EQ-5D-5L utility scores at baseline, four weeks, and six months are presented in figure 2. Adjusting for baseline differences, the mean QALYs over six months for the intervention group was 0.34 (95% CI 0.31–0.37) and 0.26 (95% CI 0.22–0.30) for the control group with a mean gain in QALYs per patient of 0.08 (95% CI 0.03–0.13). The cost of the intervention was estimated to be £1200 per patient. Costs included consultant neurology time, physiotherapy time (NHS band 7), equipment and consumables (including intervention workbook and issuing less supportive splints or walking aids for some patients only), lunch for five days and hotel accommodation for four nights (costs are itemised in online supplementary data). The cost of control was on average 4.8 sessions per patient multiplied by the cost of 1 hour of a neurophysiotherapist Band 7 (£49) or £233 per patient. Based on this data, the mean incremental cost per QALY gained was £12,087.

In the post-treatment feedback form, all participants in the intervention group reported they were either completely satisfied (86%) or satisfied (14%) with their treatment and they would be extremely likely (93%) or likely (7%) to recommend the programme to family and friends if they required similar treatment. The intensity of treatment was considered about right (38%) or very intense but manageable (48%). Treatment fidelity data is reported in online supplementary data and was considered satisfactory.

All control participants but one had been seen by a community physiotherapist in the period from baseline to six month follow up. The number of sessions ranged from 1 to 17; the median number was 5 (IQR 3–7.5). The content of physiotherapy sessions (reported by participants) included gait retraining, stair practice, balance, nonspecific cardiovascular exercise, specific strengthening exercises, and stretching. Four participants were provided

with a walking aid or splint. One participant had fatigue management education and one participant was given specific strategies aimed at controlling a functional tremor.

No serious adverse incidents were reported during the study period. Some participants from the intervention group reported exacerbation of chronic pain or fatigue during, and the week following treatment. These resolved without the need for a new intervention. No participants reported deterioration of mental health associated with treatment.

Figure 1. Trial Profile

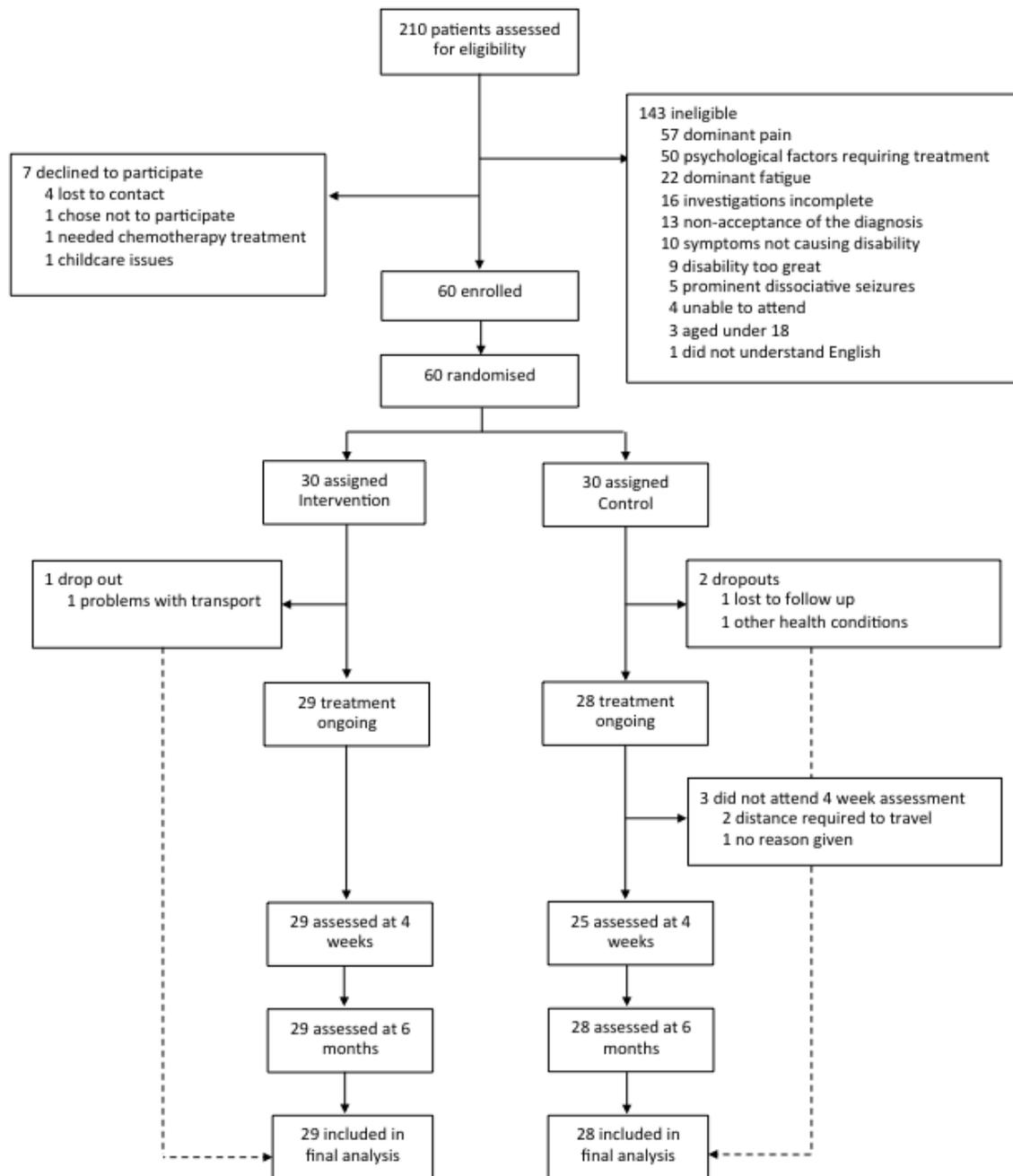


Table 1. Baseline demographic and clinical characteristics

		INTERVENTION n=30	CONTROL n=30	OVERALL
<b>DEMOGRAPHIC DATA</b>				
Age, mean (SD)		44 (13.1)	41 (13.1)	43 (13.1)
Female sex		22 (73%)	21 (70%)	43 (72%)
Marital status				
	Married/partner	19 (63%)	18 (60%)	37 (62%)
	Single	11 (37%)	12 (40%)	23 (38%)
Employment status				
	In paid work or full time study	14 (48%)	12 (40%)	26 (43%)
	Not working due to ill health	14 (45%)	15 (50%)	29 (48%)
	Retired	2 (7%)	3 (10%)	5 (8%)
Education level				
	Less than 16 years	2 (7%)	1 (3%)	3 (5%)
	Up to 16 years	8 (27%)	13 (43%)	21 (35%)
	Up to 18 years	4 (13%)	6 (20%)	10 (17%)
	Degree level qualification	13 (43%)	9 (30%)	22 (37%)
	Post graduate qualification	3 (10%)	1 (3%)	4 (7%)
<b>CLINICAL DATA</b>				
Symptom duration in years, mean (SD)		5.9 (8.3)	5.6 (6.2)	5.8 (7.3)
Age at symptom onset, mean (SD)		38 (12.9)	36 (11.2)	37 (12.0)
Primary Symptom, frequency:				
	Weakness	3 (10%)	4 (13%)	7 (12%)
	Gait disturbance	9 (30%)	7 (23%)	16 (27%)
	Upper limb tremor	3 (10%)	3 (10%)	6 (10%)
	Head tremor	2 (7%)	1 (3%)	3 (5%)
	Fixed dystonia	0	1 (3%)	1 (2%)
	Jerks	2 (7%)	1 (3%)	3 (5%)
	Mixed movement disorder	11 (37%)	13 (43%)	24 (40%)
Sensory Symptoms, frequency				
	Visual disturbance	11 (37%)	12 (40%)	23 (38%)
	Hearing difficulties	8 (27%)	6 (20%)	14 (23%)
	Pins and needles	15 (50%)	23 (77%)	38 (63%)
	Numbness	14 (47%)	20 (67%)	34 (57%)
	Dizziness	15 (50%)	14 (47%)	29 (48%)
Other Symptoms / Complaints:				
	Weakness*	20 (67%)	23 (77%)	43 (72%)
	Headache	14 (47%)	22 (73%)	36 (60%)
	Sleep disturbance	18 (62%)	20 (67%)	38 (63%)
	Gastrointestinal complaints	9 (30%)	6 (20%)	15 (25%)
	Bladder problems	9 (31%)	11 (37%)	20 (33%)
	Speech disturbance	13 (43%)	16 (53%)	29 (48%)
	Concentration or attention problems	23 (77%)	22 (73%)	45 (75%)
	Dissociative seizures	6 (20%)	3 (10%)	9 (15%)
Pain self rating	None	6 (20%)	1 (3%)	7 (12%)
	Slight to moderate	10 (34%)	14 (47%)	24 (40%)
	Severe to extreme	13 (45%)	15 (50%)	28 (47%)
Fatigue self rating	None	2 (7%)	1 (3%)	3 (5%)
	Slight to moderate	13 (43%)	14 (47%)	27 (45%)
	Severe to extreme	15 (50%)	15 (50%)	30 (50%)
Patients reporting falls		10 (33%)	19 (63%)	29 (48%)
Previous physiotherapy		23 (77%)	23 (77%)	46 (77%)
Previous psychological therapy		9 (31%)	10 (33%)	19 (32%)

\* Including participants who reported weakness that was in addition to their primary symptom (e.g. gait disturbance and subjective complaint of weakness)

Table 2. Continuous outcome measure scores at baseline and 6 month follow up

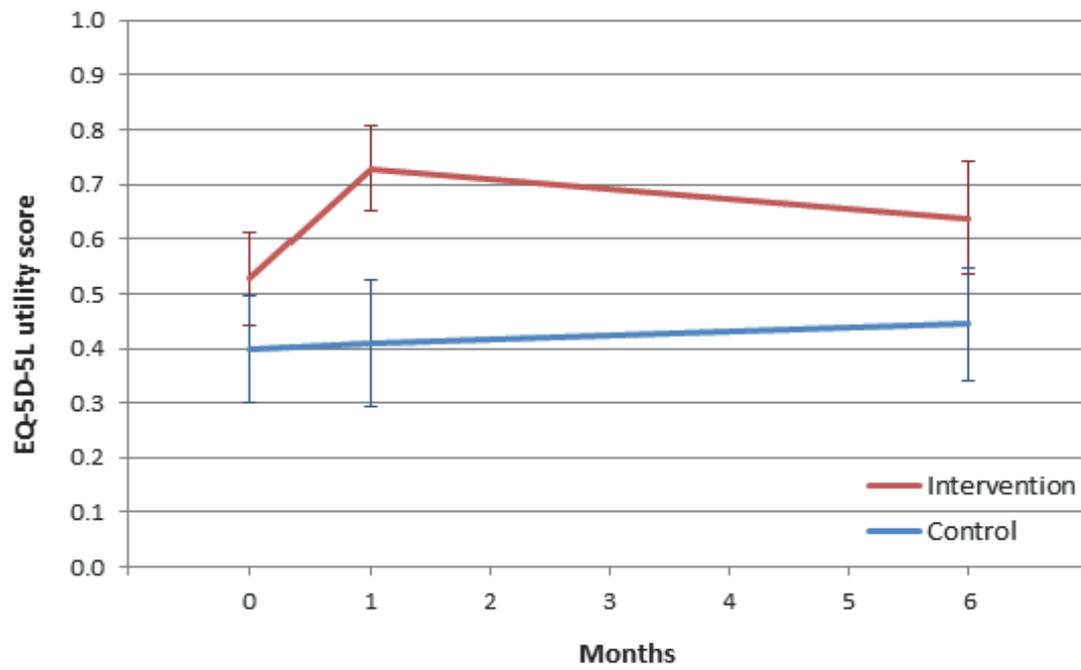
	Intervention Group mean (SD)		Control Group mean (SD)		Regression coefficient for group, baseline as covariate (95% CI)		Cohen's <i>d</i>
	BASELINE	FOLLOW UP	BASELINE	FOLLOW UP			
SF36 Domains							
Physical function	34.8 (23.7)	51.9 (27.2)	23.7 (19.0)	23.2 (21.3)	<b>19.8</b>	(10.2, 29.5)	0.70
Physical Role	31.7 (28.9)	47.0 (30.3)	19.4 (21.7)	26.8 (22.5)	<b>13.0</b>	(0.8, 25.2)	0.46
Bodily Pain	45.6 (33.5)	47.4 (33.1)	32.1 (25.3)	33.9 (27.4)	3.6	(-8.0, 15.3)	0.12
General Health	47.3 (23.9)	54.1 (28.3)	40.7 (23.4)	39.6 (22.6)	9.0	(-0.1, 18.2)	0.34
Vitality	32.3 (21.4)	39.2 (27.3)	26.6 (17.6)	28.3 (20.2)	6.2	(-3.6, 15.9)	0.25
Social Function	39.7 (33.2)	56.9 (30.2)	34.4 (29.8)	37.0 (25.1)	<b>17.1</b>	(5.0, 29.2)	0.58
Role Emotional	70.1 (29.5)	68.7 (34.5)	61.0 (32.6)	62.5 (35.4)	0.1	(-15.1, 15.4)	0.00
Mental Health	65.5 (21.1)	67.9 (23.8)	58.4 (23.8)	59.3 (25.2)	3.4	(-6.4, 13.2)	0.14
Physical Summary score	33.1 (11.1)	38.7 (10.8)	28.7 (7.9)	29.5 (9.2)	<b>5.9</b>	(2.1, 9.7)	0.54
Mental Summary score	45.2 (13.0)	45.9 (13.6)	42.6 (13.3)	43.3 (14.2)	0.9	(-4.9, 6.8)	0.06
HADS Anxiety	6.5 (3.8)	6.9 (4.8)	7.7 (4.9)	7.9 (5.6)	-0.1	(-2.1, 2.0)	-0.02
HADS Depression	5.4 (4.0)	5.2 (3.9)	8.0 (4.5)	8.4 (5.0)	-1.4	(-3.2, 0.5)	-0.30
WSAS	24.7 (7.9)	20.2 (10.5)	27.6 (7.5)	26.9 (10.2)	-4.2	(-8.4, 0.1)	-0.39
Berg Balance Scale	39.0 (13.8)	47.7 (13.8)	35.7 (13.2)	37.0 (14.7)	<b>8.0</b>	(2.9, 13.1)	0.53
10 metre walk time *	16.8 (10.0)	9.6 (3.8)	24.6 (17.3)	19.0 (10.6)	<b>-6.7</b>	(-10.7, -2.8)	-0.72
Functional Mobility Scale	11.7 (4.1)	14.5 (3.5)	10.0 (3.6)	10.0 (3.9)	<b>3.4</b>	(1.9, 5.0)	0.79
DASH	51.8 (19.6)	39.6 (25.6)	51.2 (15.0)	48.1 (21.4)	<b>-9.1</b>	(-17.4, -0.8)	-0.38
B-IPQ composite score	50.0 (10.8)	39.4 (16.1)	54.6 (10.6)	51.0 (13.0)	<b>-8.0</b>	(-14.4, -1.6)	0.51

\* 2 outliers removed from the intervention group (baseline times of 197 and 182 seconds). Removing these outliers decreased the treatment effect by 1.4 seconds. **Higher scores represent better health** in the SF36, Berg Balance and Functional Mobility Scale. **Higher scores represent worse health** for HADS, Work and Social Adjustment, 10 metre timed walk and DASH. Abbreviations: HADS=Hospital Anxiety and Depression Scale; WSAS=Work and Social Adjustment Scale; DASH=Disabilities of Arm Shoulder and Hand.

Table 3. Clinical Global Impression Scale at 6 months. We defined a good outcome as a rating of improved or much improved, and a poor outcome as a rating of no change, worse or much worse.

	Intervention Group	Control Group
Much worse	0	3 (11%)
Worse	1 (3%)	6 (21%)
No change	7 (24%)	14 (50%)
Improved	11 (38%)	5 (18%)
Much improved	10 (35%)	0
<b>Collapsed Scores</b>		
Good Outcome	21 (72%)	5 (18%)
Poor Outcome	8 (28%)	23 (82%)

Figure 2. Mean EQ-5D-5L utility scores at baseline, four weeks and six months for the intervention and control groups. A utility score of 1.0 represents full health.



## DISCUSSION

We report a large randomised feasibility study of a specific physiotherapy-based treatment for FMS. Recruitment rate, enrolment and retention were high and clinical outcomes were promising, providing evidence that an appropriately powered RCT is feasible, timely and important. Thirty-two per cent of new patients presenting to our clinics with FMS met the selection criteria and there was a 90% enrolment rate. Given the high prevalence of such patients in general neurology clinics it follows that there are sufficient patients to run a larger version of this trial.[1,2] High rates of recruitment and retention point to the intervention being acceptable, supported by participant feedback forms.

An important aim was to test the utility of a range of outcome measures and determine which to use in a power calculation for a future clinical trial. Measuring outcome in FMS is complicated by the variable nature of symptom severity inherent to the diagnosis. For this reason, snapshot measures of disability are likely to have problems with test-retest reliability, limiting their usefulness. Gait and balance outcome measures are restrictive as they are not applicable to patients with upper limb symptoms only. The SF36 Physical Function domain was the most promising primary outcome. It had a medium to large effect size ( $d=0.70$ ), and it is not as vulnerable to symptom fluctuation, as answers are given based on the respondent's perception of the average experience within the set recall period.

There were no reported serious adverse incidents during the trial period. We did not identify any mental health related adverse events associated with physiotherapy treatment. Patients with clinically evident anxiety and depression warranting intervention were excluded from the study and referred to more appropriate treatment. Measures of mental health did not change in either group. Some participants in the intervention group reported an exacerbation of chronic fatigue related to the intensity of treatment, which resolved spontaneously over several days. We suspect the relatively high intensity and short duration is an important therapeutic element of our intervention, allowing gains made in therapy to be built upon in subsequent sessions, minimising time for symptom relapse or interference from environmental symptom maintaining factors. This intensity may make it unsuitable for some patients and with this in mind we excluded those for whom chronic pain or fatigue was

the dominant problem. Despite this, half the enrolled participants still rated their pain and fatigue as severe to extreme.

To our knowledge, this is the first reported randomised study of physical rehabilitation for FMS with a control period greater than four weeks. With the caveat that this research was primarily designed to assess feasibility, we report a moderate to large treatment effect size across a range of measures of physical function, controlled over a six month period. A larger proportion of the intervention group rated their symptoms as improved (72%) compared to the control group (18%), while 32% of the control group felt their symptoms had worsened over the follow up period, compared to 3% in the intervention group. The effect size of the intervention is consistent with those of similar published studies in FMS, including our cohort study of 47 patients during the development phase of the five day programme;<sup>[8]</sup> a five day physiotherapy and occupational therapy based intervention;<sup>[26]</sup> and a randomised delayed-start trial of a three week inpatient physical based rehabilitation programme.<sup>[5]</sup> The improvement reported in the current study occurred in a sample of patients with characteristics usually associated with a poor prognosis. The average FMS duration was 5.8 years (SD 7.3), participants had multiple coexisting symptoms, and high rates of unemployment due to ill health. It is possible that if the intervention occurred earlier in the course of their disorder, it may have been more effective.

The B-IPQ total score is thought to represent the threat value of an illness. In our study, the intervention was associated with a reduction in the B-IPQ total score in the intervention group and there was little change in the control group (table 2). We hypothesise that the intervention helped patients to understand their symptoms and improve control over their movement, both of which resulted in diminished concern. This may represent one mechanism by which the intervention affects change, although we recognise that the total B-IPQ score may have problems with internal consistency.<sup>[27]</sup>

The EQ-5D-5L is the preferred instrument for generating QALYs by the UK organisation the National Institute for Health and Care Excellence (NICE). The average difference in QALYs between the groups adjusting for baseline differences was 0.08 QALYs and the resulting ICER of £12,087 suggests the intervention is most likely cost effective. In general, an ICER below £20,000 is considered cost effective.<sup>[28]</sup> This is without accounting for a potential reduction

in the costs of health and social care utilisation, reduction in disability benefits and return to paid employment.

We recognise a number of limitations in our study. It was not specifically designed or powered to detect a treatment effect. However, given the absence of controlled trials in the literature we considered reporting outcome appropriate. At baseline, the control group had scores that represented worse health than the intervention group. Our analysis accounted for baseline differences and there was still a large treatment effect with the intervention and little or no change with the control condition. A future trial could consider a randomisation procedure that involved minimisation to account for baseline severity. Participants and assessors were not masked to treatment allocation, which may have introduced bias. Most outcomes were subjective patient reported outcomes, which may be influenced by many factors, including the lack of blinding. We did not use a standardised diagnostic schedule to ascertain clinically significant anxiety or depression as a basis for exclusion from the study. This may have led to exclusion of some patients who might have benefitted from the programme. The intervention included an additional consultation with the study neurologist that was not offered to the control group. This may have enhanced the therapeutic benefit of the intervention, limiting generalisability to services where this is unavailable. Finally we did not standardise the control condition. A strength of the study is that the selection criteria were relatively inclusive (we did not exclude on the basis of age, FMS duration, or phenomenology), making results more transferable to a real world clinical context.

In summary, this study demonstrates the feasibility of performing a large trial of specialist physiotherapy for FMS. We report a large treatment effect and evidence of cost benefit in a group of patients that are prevalent, have poor quality of life and have a poor prognosis with the current available treatment. The study data strongly support the need for a multicentre randomised trial of this intervention.

## **AUTHORS' CONTRIBUTIONS**

Glenn Nielsen and Mark Edwards devised the physiotherapy treatment programme. The following authors contributed to the design of the study: Glenn Nielsen, Mark Edwards, Marta Buszewicz, Fiona Stevenson, Eileen Joyce, Rachael Hunter, Luciana Ricciardi, and Jonathan Marsden. Kate Holt delivered the intervention. Magda Dudzic completed data collection. Glenn Nielsen completed data analysis. Rachael Hunter completed health economic analysis. Glenn Nielsen and Mark Edwards prepared the first draft of the manuscript, all authors reviewed and revised the subsequent versions of the manuscript.

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