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Which factors predict outcome from specialist physiotherapy for functional motor disorder? Prognostic modelling of the Physio4FMD intervention

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ABSTRACT

Objectives: Physiotherapy is considered part of first line treatment for functional motor disorder (FMD) although not all patients benefit. Predictors of treatment outcome may help to inform triage decisions. We aimed to determine which baseline variables predicted treatment outcome in the pragmatic multicentre Physio4FMD randomised controlled trial of specialist physiotherapy for FMD.

Methods: Participants randomised to the specialist physiotherapy arm of the trial were included in the analysis. Treatment outcome was dichotomised into improvement vs no improvement, based on two measures, Short Form 36 Physical Functioning (SF36 PF) and participant-rated Clinical Global Impression Scale of Improvement (CGI-I). Predictors of outcome were selected from baseline variables. Univariate logistic regression was used to calculate the odds ratio of improvement for each variable. Variables associated with improvement at $p < 0.1$ were considered for inclusion in a multiple logistic regression model.

Results: A greater perception of having control over recovery predicted improvement on the CGI-I (OR 1.18, 95 % CI 1.07, 1.31). Predictors of lack of improvement were an increased perception of the permanence of symptoms, predicting lack of improvement on the SF36 PF (OR 0.91, 95 % CI 0.84, 0.99) and older age, predicting lack of improvement on the CGI-I (OR 0.97, 95 % CI 0.95, 0.998).

Conclusions: Age and perceptions of symptom control were weak predictors of outcome from specialist physiotherapy. In contrast, a number of factors commonly believed to predict poorer treatment response, including illness duration and levels of pain and fatigue, were not related to the outcomes measured in this study.

Abbreviations: CGI-I, Clinical Global Impression Scale of Improvement; FND, Functional Neurological Disorder; FMD, Functional Motor Disorder (a subset of FND); RCT, Randomised Controlled Trial; SF36, Short Form 36 questionnaire; TAU, Treatment as Usual.

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1. Introduction

Patients with functional neurological disorder (FND) experience symptoms such as limb weakness, sensory disturbance and seizures, usually in combination with other symptoms such as chronic pain and fatigue [1]. Physiotherapy is considered an important part of treatment for the motor symptoms of FND, although evidence for its efficacy has been limited [2].

Physio4FMD was a multicentre randomised controlled trial (RCT) of specialist physiotherapy for the motor symptoms of FND, in this paper referred to as functional motor disorder (FMD) [3]. The trial compared a specialist physiotherapy programme comprising nine sessions and a follow-up session at three months, to treatment as usual (TAU) physiotherapy, which was a referral to the local community physiotherapy service for people with neurological disorders. The primary RCT outcome, the Physical Functioning domain of the Short Form 36 (SF36) questionnaire at 12-months was not significantly different between groups. However, several secondary outcomes favoured specialist physiotherapy, including the participant rated Clinical Global Impression Scale of Improvement (CGI-I), where participants rated the change in their movement problem on a five-point Likert scale, from much improved to much worse. We found that 59 % of those receiving specialist physiotherapy rated their movement as improved or much improved, compared to 39 % of those in the TAU group (OR 2.3, 95 % CI 1.4 to 3.9). The proportion of study participants who reported their movement as very much improved was 26 % in the specialist physiotherapy group and 14 % in the TAU group. These data suggest that there is a proportion of people with FMD for whom specialist physiotherapy is more suited. Understanding who is most likely to benefit from treatment prior to starting would inform more efficient utilisation of limited resources and improve patient experiences.

A systematic review of prognosis of FMD (regardless of treatment), found mixed results [4]. Longer duration of symptoms was the most reliable predictor of worse outcome, although clinicians involved in treatment of people with FMD report that some patients with long symptom durations can do well with treatment. The impact of psychiatric comorbidity on prognosis was equivocal. From eight studies exploring this relationship, six found that prognosis was negatively influenced by psychiatric comorbidity and two studies found a positive effect on outcome. Other characteristics that were inconsistently found to be associated with outcome were change in marital status (improved outcome), impaired perception of social life (worse outcome), pending litigation (worse outcome), and lower confidence in the FMD diagnosis (worse outcome). These variables may be related to other contextual factors; for example, it was suggested that co-existing anxiety that responds to treatment may sometimes result in synergistic improvement of FMD symptoms.

A handful of studies have explored predictors of outcome from FMD-specific treatment. These data must be interpreted with caution as the studies were limited by small sample sizes, varying ways of assessing outcome, varying statistical analytical approaches and lack of corrections made for multiple comparisons. From seven studies that explored variables associated with outcome from rehabilitation for FMD [5–11]; good outcomes were associated with female gender in two studies [5,6] and no relationship with gender was found in another two studies [9,10]; acute onset (<1 month) in one study [10]; older age in one study [8]; and higher confidence in the treatment in one study [11]. Worse outcomes were described in one study when patients were admitted to rehabilitation from a hospital ward or a nursing home [7]; and another study found patients who had a history of abuse or physical trauma had smaller improvements [8]. No relationships were found between treatment outcome and the following baseline measures: symptom duration [5,6,8,9,11], anxiety or depression [5,6,9,11], physical disability [7,11], employment status [9], and marital status [9]. The impact of anxiety and depression on outcome was explored in a meta-analysis involving 348 patients from eight mixed-treatment studies [12]. Neither anxiety nor depression was found to influence treatment outcome in the pooled results.

Against this background, the aim of this study was to explore which baseline characteristics predicted outcome from the specialist physiotherapy intervention in the Physio4FMD RCT as measured by two treatment outcomes (SF36 Physical Functioning and CGI-I).

2. Methods

2.1. Participants

Participants were adults (aged 18 or over) diagnosed with FMD by a participating neurologist from one of the 11 trial sites. Potential participants gave informed consent to participate before being randomised to either the specialist physiotherapy condition or treatment as usual physiotherapy. Participants who were randomised to the specialist physiotherapy intervention were included in this analysis. Participants who were unable to receive treatment due to COVID-19 lockdowns were excluded, as defined and described in the analysis plan [13]. Participants who were randomised to treatment as usual were also excluded. Baseline assessments were completed during a face-to-face appointment with a research assistant. Follow-up data were self-reported at 12-months post randomisation via the participant's preference from an online form, paper and pen using return mail, or by telephone with a blinded research assistant. The Physio4FMD protocol and trial outcomes paper provides a detailed account of the trial methodology [3,14].

2.2. Specialist physiotherapy intervention

Prior to randomisation, the diagnosis of FMD was communicated to participants by the diagnosing neurologist. The neurologists' explanation for FMD included how the diagnosis was made based on the presence of positive clinical signs [3]. The specialist physiotherapy intervention was conducted over 9 sessions which were completed within three-weeks and a follow-up session at three-months. Treatment was tailored to the individual and followed an interactive workbook that was completed together by the physiotherapist and participant. The aims of treatment were to help the patient to understand their symptoms, to retrain movement with a redirected focus of motor attention, and to develop a self-management plan [3].

2.3. Outcome measures and variables

For the purposes of the current study, improvement from treatment was determined using two outcome measures, the Physical Functioning domain of the SF36, and the Clinical Global Impression Scale of Improvement (CGI-I). The SF36 Physical Functioning domain comprises 10 items that ask about difficulty with activities of daily living and mobility; the score range is 0–100, with a lower number being worse [15]. The score was dichotomised into improved vs no improvement with the cut-off for improvement at 12-months set at a 10-point increase from baseline score. The minimum clinically important difference for the SF36 has not been established in FMD; we therefore chose the conservative cut-off score of 10-points based on findings from other conditions [3,16]. The CGI-I asked participants to respond to the statement, "After physiotherapy, the problem with my movement is…". Response options were selected from a Likert scale (much improved, improved, no change, worse, or much worse) [3]. The outcome was dichotomised into improved (ratings of much improved and improved) vs no improvement (ratings of no change, worse and much worse). The decision to dichotomise the outcome measures was made prior to analysis.

Predictors of outcome from the scales described above were explored from baseline demographic and clinical variables. Demographic variables included age, sex, ethnicity, marital status, employment status, education, past medical history, previous treatments, dominant motor symptom type, and symptom duration (see Tables 1 and 2 for the full

Table 1
Univariate logistic regression model of improvement based on a 10-point increase in score from baseline to 12-months in the SF36 Physical Functioning domain.

Variable	Improved score (N = 67)	No change or worse (N = 71)	OR	95 % CI	p-value
	n/N (%) or mean (SD)	n/N (%) or mean (SD)			
Age	44.3 (12.9)	45.8 (15.7)	0.993	[0.970, 1.016]	0.537
Male	15/67 (22.4 %)	20/71 (28.2 %)	1.000	[0.628, 2.945]	0.436
Female	52/67 (77.6 %)	51/71 (71.8 %)	1.359		
Ethnicity - White	66/67 (98.5 %)	58/71 (81.7 %)	1.000	[0.009, 0.533]	0.011
Ethnicity - Non-white	1/67 (1.5 %)	13 (17.2 %)	0.068		
Married/ cohabitating	37/67 (55.2 %)	38/71 (53.6 %)	1.000		
Divorced/ widowed	6/67 (9.0 %)	6/71 (8.4 %)	1.027	[0.304, 3.474]	0.964
Single	24/67 (35.8 %)	27/71 (38.0 %)	0.913	[0.448, 1.861]	
Living alone - No	54/64 (84.4 %)	60/69 (87.0 %)	1.000	[0.467, 3.266]	0.671
Living alone - Yes	10/64 (15.6 %)	9/69 (13.0 %)	1.235		
Has dependents - No	39/67 (58.2 %)	48/71 (67.6 %)	1.000	[0.333, 1.337]	0.254
Has dependents - Yes	28/67 (41.8 %)	23/71 (32.4 %)	0.667		
Has carers - No	44/67 (65.7 %)	40/71 (56.3 %)	1.000	[0.339, 1.343]	0.262
Has carers - Yes	23/67 (34.3 %)	31/71 (43.7 %)	0.674		
Years of Education	14.0 (3.3)	14.4 (4.3)	0.968	[0.885, 1.060]	0.489
Working or studying	29/67 (43.3 %)	23/71 (32.4 %)	1.000	[0.314, 1.256]	0.188
Not working & other categories	38/67 (56.7 %)	48/71 (67.6 %)	0.628		
PMH Cardiovascular	15/67 (22.4 %)	19/71 (26.8 %)	1.344	[0.615, 2.936]	0.458
PMH Respiratory	19/67 (28.4 %)	19/71 (26.8 %)	0.980	[0.463, 2.074]	0.957
PMH Neurology	39/67 (58.2 %)	30/71 (42.3 %)	0.567	[0.287, 1.121]	0.103
PMH Psychiatry	38/67 (56.7 %)	39/71 (54.9 %)	1.026	[0.519, 2.029]	0.940
PMH Genitourinary	21/67 (31.3 %)	32/71 (45.1 %)	1.947	[0.965, 3.930]	0.063
PMH Gastrointestinal	21/67 (31.3 %)	28/71 (39.4 %)	1.533	[0.756, 3.109]	0.236
PMH Musculoskeletal	34/67 (50.8 %)	44/71 (62.0 %)	1.779	[0.892, 3.549]	0.102
PMH Endocrinology	10/67 (14.9 %)	7/71 (9.9 %)	0.654	[0.233, 1.834]	0.420
PMH Other Functional	24/67 (35.8 %)	26/71 (36.6 %)	1.109	[0.551, 2.231]	0.772
PMH ENT	11/67 (16.4 %)	6/71 (8.5 %)	0.493	[0.171, 1.420]	0.190
PMH Dermatology	13/67 (19.4 %)	11/71 (15.5 %)	0.802	[0.331, 1.942]	0.624
PMH Ophthalmology	7/67 (10.5 %)	12/71 (16.9 %)	1.837	[0.675, 4.997]	0.234
PMH Other	15/67 (22.4 %)	17/71 (23.9 %)	1.156	[0.522, 2.558]	0.721
Previous physiotherapy	35/65 (53.9 %)	33/71 (46.5 %)	1		
Previous psychology	14/65 (21.5 %)	11/71 (15.5 %)	0.744	[0.379, 1.462]	0.391
Previous occupational therapy	9/65 (13.9 %)	13/71 (18.3 %)	0.668	[0.279, 1.600]	0.365
Previous botulinum toxin	0/65 (0.0 %)	1/70 (1.4 %)	1.3951	[0.553, 3.520]	0.481
Previous osteopathy	4/65 (6.2 %)	0/70 (0.0 %)			
Previous chiropractic treatment	3/65 (4.6 %)	1/70 (1.4 %)	0.300	[0.030, 2.955]	0.302
Previous acupuncture	13/66 (19.7 %)	5/71 (7.0 %)	3.238	[1.085, 9.658]	0.035
Previous hypnotherapy	4/65 (6.2 %)	0/70 (0.0 %)			
Previous cranial sacral therapy	1/65 (1.5 %)	0/70 (0.0 %)			
Previous massage	4/65 (6.2 %)	4/71 (5.6 %)	0.910	[0.218, 3.799]	
Previous pain management	6/65 (9.2 %)	7/71 (9.9 %)	1.076	[0.342, 3.384]	0.901
Previous fatigue management	2/65 (3.1 %)	2/71 (2.8 %)	0.913	[0.125, 6.676]	0.929
Previous inpatient rehab	3/65 (4.7 %)	2/70 (2.9 %)	0.598	[0.097, 3.699]	0.580
Previous other treatment	8/60 (13.3 %)	3/63 (4.8 %)	0.325	[0.082, 1.289]	0.110
Dominant Symptom Type					
Weakness	25/67 (37.3 %)	22/71 (31.0 %)	1.000		
Tremor	10/67 (14.9 %)	11/71 (15.5 %)	0.800	[0.286, 2.242]	
Gait disturbance	19/67 (28.4 %)	23/71 (32.4 %)	0.727	[0.315, 1.676]	
Jerks	2/67 (3.0 %)	4/71 (5.6 %)	0.440	[0.073, 2.639]	0.950
Dystonia	1/67 (1.5 %)	0/71 (0.0 %)			
Mixed movement disorder	9/67 (13.4 %)	9/71 (12.7 %)	0.880	[0.297, 2.610]	
Fixed functional dystonia	0/67 (0.0 %)	1/71 (1.4 %)			
Other	1/67 (1.5 %)	1/71 (1.4 %)	0.880	[0.052, 14.918]	
Confidence in the diagnosis	8.1 (2.0)	8.2 (2.0)	0.981	[0.830, 1.159]	0.818
Fatigue state Moderate, slight or no fatigue	38/67 (56.7 %)	43/71 (60.6 %)	1.000	[0.595, 0.209]	0.647
Fatigue state Extreme and severe fatigue	29/67 (43.3 %)	28/71 (39.4 %)	1.172		
Fatigue state Severe, moderate, slight or no fatigue	59/67 (88.1 %)	63/71 (88.7 %)	1.000	[0.236, 1.908]	0.902
Extreme fatigue	8/67 (11.9 %)	8/71 (11.3 %)	0.671		
Functional Mobility Scale	11.8 (3.7)	11.0 (5.1)	1.040	[0.965, 1.121]	0.305
HADS Anxiety score	10.1 (5.6)	10.4 (4.5)	0.986	[0.922, 1.055]	0.688
HADS Depression score	8.4 (4.1)	9.2 (4.0)	0.954	[0.877, 1.037]	0.265
HADS Anxiety less than 11	35/67 (52.2 %)	36/71 (50.7 %)	1.000	[0.482, 1.834]	0.857
HADS Anxiety 11 and above	32/67 (47.8 %)	35/71 (49.3 %)	0.941		

(*continued on next page*)

Table 1 (*continued*)

Variable	Improved score (*N* = 67)	No change or worse (*N* = 71)	OR	95 % CI	*p*-value
	n/N (%) or mean (SD)	n/N (%) or mean (SD)			
HADS Depression less than 11	46/67 (68.7 %)	45/71 (63.4 %)	1.000	[0.390, 1.602]	0.514
HADS Depression 11 and above	21/67 (31.3 %)	26/71 (36.6 %)	0.790		
Extended PHQ-15	16.4 (5.5)	17.4 (5.8)	0.970	[0.913, 1.031]	0.332
EQ5D5L Pain					
Moderate, slight or no pain	20/66 (30.3 %)	24/71 (33.8 %)	1.000	[0.572, 2.411]	0.661
Extreme and severe pain	46/66 (69.7 %)	47/71 (66.2 %)	1.174		
IPQ-R Identity	8.9 (2.4)	9.0 (2.9)	0.987	[0.871, 1.120]	0.843
IPQ-R Causes	40.6 (10.0)	40.5 (10.8)	1.001	[0.969, 1.034]	0.945
IPQ-R Time (Acute/ Chronic)	**20.7 (4.3)**	**22.4 (4.0)**	**0.914**	**[0.844, 0.990]**	**0.027***
IPQ-R Timeline Cyclical	14.5 (3.8)	13.9 (3.7)	1.039	[0.950, 1.137]	0.403
IPQ-R Consequences	24.1 (4.0)	23.7 (3.9)	1.027	[0.943, 1.118]	0.538
IPQ-R Personal Control	19.2 (4.0)	18.2 (3.9)	1.062	[0.974, 1.159]	0.171
IPQ-R Treatment Control	18.7 (2.7)	18.1 (2.8)	1.096	[0.962, 1.250]	0.169
IPQ-R Illness Coherence	8.0 (3.5)	8.0 (3.1)	1.000	[0.932, 1.072]	0.991
IPQ-R Emotional Representation	21.3 (5.5)	21.5 (5.0)	0.992	[0.931, 1.058]	0.814

PMH=Past Medical History; SF36 = Short Form 36 Questionnaire; HADS=Hospital Anxiety and Depression Scale IPQ-R = Revised Illness Perception Questionnaire.

* Included in the final multiple logistic regression model.

list). Baseline clinical variables examined for their prognostic value were the Extended Patient Health Questionnaire 15 [14,17], the Revised Illness Perception Questionnaire (IPQ-R) subscales (Identity, Causes, Timeline, Timeline Cyclical, Consequences, Personal Control, Treatment Control, Illness Coherence, and Emotional Representation) [18], and the Hospital Anxiety and Depression Scale (HADS) [19]. We took an inclusive approach to this first exploratory stage of potential prognostic factors as we were open to finding new potential predictors of outcome; additionally previous research has not found consistent prognostic factors to inform the analysis, and theoretical assumptions about which factors may predict outcome are at risk of being influenced by prejudice and stigma.

The HADS scores were dichotomised into scores of 0–10 vs 11 and above, the latter group representing probable cases of anxiety or depression [19]. This decision was made to aid clinical interpretation of the findings, as the influence of a one-point increase on the HADS scale on the odds ratio of improvement has less clinical utility than knowing whether the presence of anxiety or depression influences outcome/potential benefit from treatment. SF36 domains were not considered for predictor variables because they are composite measures of health which can be difficult to interpret. In addition, they are rarely used clinically and therefore they were considered to have low clinical utility for prognostication.

2.4. Statistical analysis

Descriptive statistics were calculated for baseline variables, with the frequency and percentage of participants with improvement on the two outcomes of interest. In a first exploratory stage, univariate logistic regression was used to calculate an odds ratio of improvement (with 95 % confidence intervals) on the two outcomes for all included baseline variables. Clinical judgments were then used to determine the variables for inclusion in the final model. For variables that were highly correlated, only the variable deemed to have greater clinical utility was included. In stage two, variables associated with improvement at $p < 0.1$, after clinical judgments were exercised, were included in a multiple logistic regression model [20]. Backward elimination methods were chosen for the variable selection due to its advantage of assessing the joint predictive ability of potential predictors (i.e. when variables influence the outcome above and beyond the impact of their individual influences) [21]. Additionally, it allows variables correlated with other variables that may confound the relationship between potential predictors and the outcome to be removed from the final model [21]. The methods were applied to eliminate variables with p-value>0.05 in the multiple logistic regression models. At each step, the variable with largest p-value greater than 0.05 was removed from the multiple logistic regression model until only variables significant at 0.05 level remained. The final multiple logistic regression models included all variables associated with each outcome and are considered prognostic factors. Analyses were performed using Stata version 18.

3. Results

Recruitment for the Physio4FMD RCT occurred between October 2018 and January 2022, with a 17-month break during the COVID-19 pandemic (March 2020 to July 2021). From a total of 355 recruited to the study, 179 were assigned to specialist physiotherapy (50 %). Treatment in this group was interrupted by COVID-19 lockdowns for 27 participants and their data were excluded from this analysis. Data were missing for an additional 14 participants, leaving 138 in the analysis (91 % retention, not including those affected by COVID-19).

3.1. Improvement at 12-months

Based on a 10-point increase in SF36 PF score, 49 % (67/138) had a clinically significant improvement. Using the CGI-I outcome measure, 59 % (81/138) reported improvement. Thirty-seven percent (37 %, 51/138) improved on both scales and 70.3 % (97/138) improved on at least one of the scales (see Fig. 1).

3.2. Univariate analysis

Odds ratios for baseline univariate predictors of improvement on each outcome measure are presented in Tables 1 and 2.

3.3. Multiple logistic regression analysis for SF36 physical functioning

Amongst the variables that were significant at $p < 0.1$, ethnicity was excluded from the model due to the small number of participants identifying as non-white (14/138, with 1 person improving and 13 not improving). Previous acupuncture treatment was also excluded due to low numbers (18/138, with 13 improving and 5 not improving). After backwards elimination of variables with a p-value>0.05, the final logistic regression model included only IPQ-R Time (acute/chronic) (OR 0.91, 95 % CI 0.84, 0.99, $p = 0.027$). This indicated that a greater perception that FMD symptoms are likely to be permanent predicted a lack of a clinically significant improvement on the SF36 Physical Functioning domain. See Table 3.

3.4. Multiple logistic regression analysis for CGI-I

Previous physiotherapy treatment was excluded from the model prior to analysis due to potential correlations with illness severity. After backwards elimination of variables with a p-value>0.05, the final

Table 2
Univariate logistic regression model of improvement based on the Clinical Global Impression Scale of Improvement (participant perception, scores of improved or much improved).

Variable	Improvement reported ($N = 81$)	No change or worse ($N = 57$)	OR	95 % CI	p-value
	n/N (%) or mean (SD)	n/N (%) or mean (SD)			
Age	**42.6 (13.9)**	**48.5 (14.5)**	**0.971**	**[0.947, 0.995]**	**0.019***
Male	18/81 (22.2 %)	17/57 (29.8 %)	1.000		
Female	63/81 (77.8 %)	40/57 (70.2 %)	1.488	[0.687, 3.220]	0.314
Ethnicity - White	74/81 (91.4 %)	50/57 (87.7 %)	1.000		
Ethnicity - Non-white	7/81 (8.6 %)	7/57 (12.3 %)	0.676	[0.223, 2.045]	0.488
Married/cohabitating	43/81 (53.0 %)	32/57 (56.1 %)	1.000		
Divorced/widowed	4/81 (5.0 %)	8/57 (14.0 %)	0.372	[0.103, 1.344]	0.117
Single	34/81 (42.0 %)	17/57 (29.8 %)	1.488	[0.710, 3.121]	
Living alone - No	67/79 (84.8 %)	47/54 (87.0 %)	1.000		
Living alone - Yes	12/79 (15.2 %)	7/54 (13.0 %)	1.203	[0.441, 3.282]	0.719
Has dependants - No	51/81 (63.0 %)	36/57 (63.2 %)	1.000		
Has dependants - Yes	30/81 (37.0 %)	21/57 (36.8 %)	0.992	[0.491, 2.001]	0.981
Has carers - No	51/81 (63.0 %)	33/57 (57.9 %)	1.000		
Has carers - Yes	30/81 (37.0 %)	24/57 (42.1 %)	0.809	[0.405, 1.617]	0.548
Years of Education	14.3 (4.4)	14.0 (2.8)	1.023	[0.933, 1.121]	0.627
Working or studying	36/81 (44.4 %)	16/57 (28.1 %)	1.000		
Not working & other categories	45/81 (55.6 %)	41/57 (71.9 %)	0.488	[0.236, 1.007]	0.052
PMH Cardiovascular	21/81 (25.9 %)	13/57 (22.8 %)	0.802	[0.362, 1.777]	0.587
PMH Respiratory	22/81 (27.2 %)	16/57 (28.1 %)	0.993	[0.465, 2.123]	0.986
PMH Neurology	43/81 (53.1 %)	26/57 (45.6 %)	0.683	[0.344, 1.356]	0.275
PMH Psychiatry	44/81 (54.3 %)	33/57 (57.9 %)	1.062	[0.533, 2.119]	0.863
PMH Genitourinary	30/81 (37.0 %)	23/57 (40.4 %)	1.082	[0.538, 2.177]	0.824
PMH Gastrointestinal	29/81 (35.9 %)	20/57 (35.1 %)	0.913	[0.448, 1.861]	0.803
PMH Musculoskeletal	44/81 (54.3 %)	34/57 (58.7 %)	1.142	[0.571, 2.284]	0.707
PMH Endocrinology	8/81 (9.9 %)	9/57 (15.8 %)	1.641	[0.591, 4.553]	0.342
PMH Other Functional	27/81 (33.3 %)	23/57 (40.4 %)	1.278	[0.631, 2.587]	0.496
PMH ENT	11/81 (13.6 %)	6/57 (10.5 %)	0.717	[0.248, 2.067]	0.537
PMH Dermatology	15/81 (18.5 %)	9/57 (15.8 %)	0.788	[0.318, 1.952]	0.606
PMH Ophthalmology	12/81 (14.8 %)	7/57 (12.3 %)	0.770	[0.283, 2.097]	0.609
PMH Other	15/81 (18.5 %)	17/57 (29.8 %)	1.785	[0.803, 3.970]	0.155
Previous physiotherapy	45/80 (56.3 %)	23/56 (41.1 %)	0.542	[0.271, 1.083]	0.083
Previous psychology	16/80 (17.5 %)	11/56 (19.4 %)	1.152	[0.480, 2.767]	0.751
Previous occupational therapy	15/80 (18.8 %)	7/56 (12.5 %)	0.619	[0.234, 1.634]	0.333
Previous botulinum toxin	1/80 (1.3 %)	0/55 (0.0 %)			
Previous osteopathy	3/80 (3.8 %)	1/55 (1.8 %)	0.475	[0.048, 4.692]	0.524
Previous chiropractic treatment	3/80 (3.8 %)	1/55 (1.8 %)	0.475	[0.048, 4.692]	0.524
Previous acupuncture	12/81 (14.8 %)	6/56 (10.7 %)	0.690	[0.243, 1.963]	0.487
Previous hypnotherapy	1/80 (1.3 %)	3/55 (5.5 %)	4.558	[0.462, 45.010]	0.194
Previous cranial sacral therapy	1/80 (1.3 %)	0/55 (0.0 %)			
Previous massage	6/80 (7.5 %)	0/56 (0.0 %)	0.457	[0.089, 2.351]	0.349
Previous pain management	8/80 (10.0 %)	5/56 (8.9 %)	0.882	[0.273, 2.853]	0.834
Previous fatigue management	2/80 (2.5 %)	2/56 (3.6 %)	1.444	[0.197, 10.572]	0.717
Previous inpatient rehab	4/79 (5.1 %)	1/55 (1.8 %)	0.347	[0.038, 3.194]	0.350
Previous other treatment	9/73 (12.3 %)	2/50 (4.0 %)	0.296	[0.061, 1.435]	0.131
Dominant Symptom Type					
Weakness	31/81 (38.3 %)	16/57 (28.1 %)	1.000		
Tremor	8/81 (9.9 %)	13/57 (22.8 %)	0.318	[0.109, 0.924]	
Gait disturbance	26/81 (32.1 %)	16/57 (28.1 %)	0.839	[0.352, 1.996]	
Jerks	3/81 (3.7 %)	3/57 (5.3 %)	0.516	[0.093, 2.854]	0.421
Dystonia	1/81 (1.2 %)	0/57 (0.0 %)			
Mixed movement disorder	10/81 (12.4 %)	8/57 (14.0 %)	0.645	[0.213, 1.954]	
Fixed functional dystonia	1/81 (1.2 %)	0/57 (0.0 %)			
Other	1/81 (1.2 %)	1/57 (1.8 %)	0.516	[0.030, 8.805]	
Confidence in the diagnosis	8.3 (1.9)	7.8 (2.1)	1.120	[0.946, 1.326]	0.190
Fatigue state					
Moderate, slight or no fatigue	49/81 (60.5 %)	32/57 (56.1 %)	1.000	[0.420, 1.662]	0.609
Extreme and severe fatigue	32/81 (39.5 %)	25/57 (43.9 %)	0.836		
Fatigue state					
Severe, moderate, slight or no fatigue	73/81 (90.1 %)	49/57 (86.0 %)	1.000	[0.236, 1.908]	0.455
Extreme fatigue	8/81 (9.9 %)	8/57 (14.0 %)	0.671		
Functional Mobility Scale	11.5 (4.2)	11.2 (4.9)	1.013	[0.939, 1.092]	0.744
HADS Anxiety score	9.3 (4.9)	11.7 (5.0)	0.906	[0.843, 0.974]	0.008
HADS Depression score	8.1 (3.8)	9.7 (4.2)	0.904	[0.828, 0.987]	0.024
HADS Anxiety less than 11	47/81 (58.0 %)	24/57 (42.1 %)	1.000		
HADS Anxiety 11 and above	34/81 (42.0 %)	33/57 (57.9 %)	0.526	[0.265, 1.045]	0.067
HADS Depression less than 11	59/81 (72.8 %)	32/57 (56.1 %)	1.000		
HADS Depression 11 and above	22/81 (27.2 %)	25/57 (43.9 %)	0.477	[0.233, 0.977]	0.043
Extended PHQ-15, mean (SD)	16.6 (5.9)	17.3 (5.4)	0.977	[0.919, 1.038]	0.449
EQ5D5L Pain					
Moderate, slight or no pain	24/80 (30.0 %)	20/57 (35.1 %)	1.000	[0.611, 2.602]	0.530
Extreme and severe pain	56/80 (70.0 %)	37/57 (64.9 %)	1.261		

(*continued on next page*)

Table 2 (*continued*)

Variable	Improvement reported ($N = 81$)	No change or worse ($N = 57$)	OR	95 % CI	p-value
	n/N (%) or mean (SD)	n/N (%) or mean (SD)			
IPQ-R - Identity	8.9 (2.6)	9.1 (2.8)	0.960	[0.844, 1.091]	0.531
IPQ-R - Causes	40.4 (9.7)	40.8 (11.4)	0.996	[0.964, 1.030]	0.815
IPQ-R - Time (Acute/Chronic)	21.1 (4.6)	22.2 (4.1)	0.945	[0.874, 1.023]	0.161
IPQ-R - Timeline Cyclical	14.6 (3.8)	13.7 (3.7)	1.068	[0.974, 1.170]	0.161
IPQ-R - Consequences	23.9 (3.9)	23.9 (3.9)	0.999	[0.917, 1.089]	0.983
IPQ-R - Personal Control	**19.7 (3.8)**	**17.3 (3.7)**	**1.190**	**[1.076, 1.317]**	**0.001***
IPQ-R - Treatment Control	19.0 (2.9)	17.5 (2.4)	1.195	[1.036, 1.379]	0.014
IPQ-R - Illness Coherence	8.6 (3.4)	7.2 (2.9)	1.107	[1.025, 1.196]	0.009
IPQ-R - Emotional Representation	20.9 (5.5)	22.0 (4.8)	0.962	[0.901, 1.027]	0.244

PMH = Past Medical History; SF36 = Short Form 36 Questionnaire; HADS = Hospital Anxiety and Depression Scale; IPQ-R = Revised Illness Perception Questionnaire.
* Included in the final multiple logistic regression model.

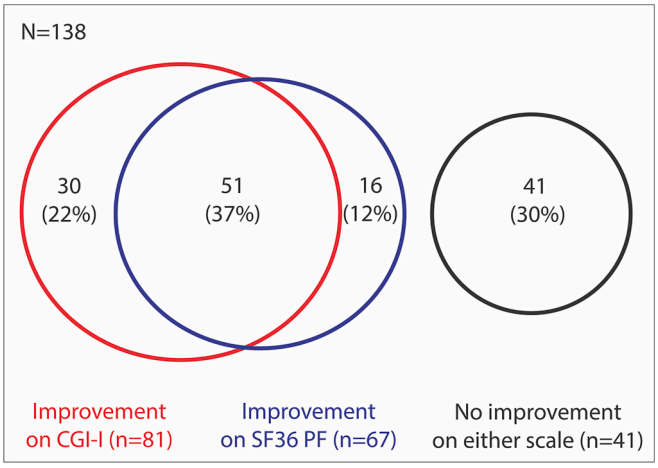

Fig. 1. Venn diagram showing the overlap between participants with improvement on Short Form 36 Physical Function domain (SF36 PF) and participant rated impression of improvement (CGI-I).

Table 3
Univariate and multiple logistic regression outcomes from baseline predictors of outcome based on a 10-point increase in the SF36 Physical Functioning domain score from baseline. Initial baseline predictors for the multiple logistic regression model were chosen based on improvement at p < 0.1 in the univariate model.a, b

Baseline variables	Univariate logistic regression		Multiple logistic regression model	
	OR [95 % CI]	p-value	OR [95 % CI]	p-value
Ethnicity (non-white)[a]	0.068 [0.009, 0.533]	0.011		
Genitourinary medical history[b]	1.947 [0.965, 3.930]	0.063		
Previous acupuncture[a]	3.238 [1.085, 9.658]	0.035		
IPQ-R Time (acute/chronic)[c]	0.914 [0.844, 0.990]	0.027	**0.914 [0.844, 0.990]**	**0.027**

IPQ-R = Revised Illness Perception Questionnaire.
Reasons for exclusion from the multiple logistic regression model:
[a] low numbers with this characteristic.
[b] *p*-value>0.05 in the multiple logistic regression model.
[c] IPQ-R Time (acute/chronic) higher scores represent a belief that symptoms will be permanent and not improve.

logistic regression model included two variables: Age (OR 0.97, 95 % CI 0.95, 0.998, $p = 0.035$) and IPQ-R Personal Control (OR 1.18, 95 % CI 1.07, 1.310, $p = 0.001$). Older age predicted lack of improvement on the CGI-I. A perception of having greater control over whether symptoms will improve (IPQ-R Personal Control, higher score) predicted improvement on the CGI-I. See Table 4. In post hoc analysis, a weak negative relationship was found between age and IPQ-R Personal Control, with a Pearson's correlation coefficient of −0.060.

4. Discussion

This study explored variables that predicted two outcomes, (i) a clinically significant improvement on the SF 36 Physical Functioning

Table 4
Univariate and multiple logistic regression outcomes from baseline predictors of outcome based on participant rated improvement on the Clinical Global Impression of Improvement Scale. Initial baseline predictors for the multiple logistic regression model were chosen based on improvement at $p < 0.1$ in univariate model.a, b

Baseline variables	Univariate logistic regression		Multiple logistic regression model	
	OR [95 % CI]	p-value	OR [95 % CI]	p-value
Age	0.971 [0.947, 0.995]	0.019	**0.972 [0.947, 0.998]**	**0.035**
Employment status: working or studying vs other[a]	0.488 [0.236, 1.007]	0.052		
Previous physiotherapy[b]	0.542 [0.271, 1.083]	0.083		
HADS Anxiety score ≥ 11[a]	0.526 [0.265, 1.045]	0.067		
HADS Depression score ≥ 11[a]	0.477 [0.233, 0.977]	0.043		
IPQ-R Personal control[c]	1.190 [1.076, 1.317]	0.001	**1.185 [1.072, 1. 310]**	**0.001**
IPQ-R Treatment control[d]	1.195 [1.036, 1.379]	0.014		
IPQ-R Illness coherence[e]	1.107 [1.025, 1.196]	0.009		

IPQ-R = Revised Illness Perception Questionnaire.
Reasons for exclusion from the multiple logistic regression model:
[a] p-value>0.05 in the multiple logistic regression model.
[b] potential correlation with illness severity.
[c] IPQ-R Personal control higher score represents the perception of having control over whether symptoms/ illness will improve.
[d] IPQ-R Treatment control higher score represents beliefs about the effectiveness of treatment in improving or controlling symptoms.
[e] IPQ-R Illness coherence higher score represents a belief of understanding one's symptoms; a lower score represents a belief that one's symptoms are puzzling and mysterious.

domain, or (ii) improvement on the CGI-I in response to the specialist physiotherapy intervention of the Physio4FMD RCT in people with FMD.

In the multiple logistic regression models, only one baseline variable predicted improvement. A greater perception of having control over improvement of symptoms (IPQ-R Personal Control) predicted a patient perception of improvement in motor symptoms (improvement on the CGI-I).

Older age predicted a lack of patient perception of improvement of motor symptoms (lack of improvement on the CGI-I). A perception of greater permanence of symptoms (IPQ-R Time acute/chronic) predicted a lack of self-reported improvement in physical functioning (lack of clinically significant improvement on the SF36 Physical Functioning domain).

Several other variables predicted outcome in univariate analysis but were not significant in multiple logistic regression models.

It was striking how many factors which are commonly considered to be relevant predictors of treatment outcomes (and therefore may be used in clinical practice as reasons to exclude patients from treatment), had no bearing on the two treatment outcomes. This list includes symptom duration, severe pain or fatigue, level of education, somatic symptom severity (PHQ-15 Extended), and dominant motor symptom classification. HADS depression "caseness" predicted a poor outcome on the CGI-I in univariate analysis but was not significant in the multiple logistic regression model. Shorter symptom duration prior to diagnosis has been found to predict a better outcome in observational studies (when outcome is collapsed into "better" vs "same" or "worse") [4], however amongst studies exploring factors predicting outcome from treatment, no relationship with symptom duration has been found. Amongst these studies outcome was defined as a binary based on the CGI-I (as per the current study) [5,6,8,11], change in blinded video-assessment of symptom severity [8], and clinician rated impression [9].

The clinical implication of our findings is that care should be taken in using broad demographic, clinical and social characteristics to exclude individuals from treatment. The odds ratios of the significant findings in this study are relatively small and therefore we would not advise that they are considered when making treatment triage decisions. Factors that are often considered to detrimentally affect treatment outcome, such symptom duration, pain, fatigue and anxiety are not supported by previous research data [5–9,11,12], where there are inconsistent and conflicting findings, nor are they supported by this study, which had the advantage of having higher methodological robustness compared to many previous studies. Whether or not these factors act as moderators and mediators of treatment outcome or influence the potential long-term benefit that can be gained from treatment, are different questions that the current study is unable to answer.

We previously reported that improvement cut-off scores for the SF36 Physical Functioning and the CGI-I captured different subsets of participants in the Physio4FMD RCT, with the CGI-I capturing more cases of improvement [3]. In total 70 % (97/138) improved on at least one of these measures. Only 37 % (51/97) improved on both measures, in other words had both a perception of improved motor symptoms (CGI-I) and improved self-reported physical function score (SF36 Physical Functioning); 22 % (30/97) improved on the CGI-I but not SF36 Physical Functioning; and 12 % (16/97) improved on the SF36 Physical Functioning but not the CGI-I. These measures did not correlate as well as expected. The discordance between participants' perception of improvement in motor symptoms (CGI-I) and change of self-reported physical function scores (SF36) highlights that these assessments capture different but related domains of health. This is further supported by our finding that each measure is associated with different baseline predictors of improvement. An alternative explanation for the discordance may lie in a previous finding that people with FMD tend to provide higher estimates of the severity of their symptoms compared to clinicians or objective measurements [22,23]. These findings highlight some of the complexity of outcome measurement in FMD.

In the multiple logistic regression model for SF36 Physical Function, only the IPQ-R Time (acute/chronic) subscale predicted outcome. This scale is derived from six items representing beliefs about the probable duration and permanence of the health problem. A higher score represents a belief that symptoms will be permanent and not improve. The odds ratio suggested that a higher score (greater belief in permanence) increased the odds of a lack of clinically significant improvement. This relationship may be interpreted as expectations for treatment influencing outcome. In which case, interventions that are aimed at positively influencing beliefs about the possibility of symptom improvement may have therapeutic value. An alternative point of view is that such individuals had realistic expectations. FMD is often described as symptoms that are potentially reversible. However, for many FMD is a chronic condition and resolution with a short duration physiotherapy intervention is unlikely.

Two baseline variables predicted outcome on participant reported CGI-I binary categories. Firstly, older age predicted a worse outcome on the CGI-I. One previous study found an association between age and outcome, but the direction of the relationship was the opposite, with older patients having greater improvements in motor symptom severity [8]. In this study of 31 people receiving inpatient multidisciplinary treatment for FMD, the association with age was found for change in blinded video assessment of motor symptom severity, but there was no association for change on a CGI-I scale. Additionally, the association with age existed immediately after treatment only, it was not present at follow up (median of 5 months) and may have been explained by confounding factors (older participants tended to have worse scores at baseline and therefore greater potential for change).

Secondly, a greater score on the IPQ-R Personal Control subscale (a greater perception of control over whether symptoms will improve, derived from six items) predicted improvement on the CGI-I. This mirrors the finding that a perception of permanence was associated with lack of improvement on SF36 Physical Functioning. Interpreting these relationships is difficult. A previous study found a similar relationship between the IPQ-R scale of Treatment Control (a belief that treatment will help to improve symptoms) and multidisciplinary rehabilitation outcome for mixed FND symptoms [11]. A similar finding was also reported in a 12-month follow-up study of 716 patients presenting to neurology with functional disorders and related conditions [24]. This study found that an expectation of non-recovery at baseline predicted a poor outcome at 12-months follow up (CGI-I ratings of no change, worse, or much worse; OR 2.22, 95 % CI 1.51, 3.26). Together these findings might support the idea that patient views about recovery and ability to influence the course of their illness can positively affect treatment outcome. In which case, perceptions and expectations about symptoms and control over symptoms could be important mediators and moderators for change and therefore targets for interventions. Alternatively, the relationship between a more optimistic perception and a better outcome may simply reflect an individual's correct perception of the severity and complexity of their condition.

As both age and perception of control over symptoms predicted a negative outcome on the CGI-I, we calculated the correlation between age and the IPQ-R Personal control score to determine if older age was associated with a perception of having less control over symptoms. The correlation, although statistically significant, was very weak, and therefore has questionable clinical significance. Other factors which may account for this relationship include the existence of other co-existing health problems that may accumulate with older age.

We acknowledge that our study had several limitations. The prognostic factors found in this study are related to the specialist physiotherapy intervention and participants of the Physio4FMD RCT and generalisability to other treatments and populations cannot be assumed. Measuring the impact of treatment in a binary outcome and our choice of outcome measures may have influenced which variables predicted outcome. We found that outcomes were worse for participants identifying as ethnically non-white, however there were insufficient numbers to further explore this statistical relationship. Our study relied on self-

report outcomes and lacked objective or clinician assessed outcome measures for comparison. Our study and others have reported conflicting findings for prognostic markers for treatment, which may indicate that despite our study being the largest physical intervention study for FMD, even larger numbers are needed for more reliable post-hoc analysis. Including the Physio4FMD participants who were assigned treatment as usual would have increased our sample size; however, it would have added heterogeneity to the treatment condition which may have influenced which characteristics did/did not predict outcome. Finally, our clinical and demographic variables do not include social factors that may influence outcome. For example, conflict at work and in the home, or the health of family members may be important determinants of health and treatment outcome that are not considered here.

5. Conclusion

In summary we found that predictors of outcome from specialist physiotherapy were older age (worse outcome), a greater perception that symptoms will be permanent (worse outcome), and a greater perception of having control over whether symptoms will improve (improved outcome). Notably, symptom duration, anxiety, depression, pain and fatigue were not associated with treatment outcome in this study.

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CRediT authorship contribution statement

Glenn Nielsen: Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Data curation. **Teresa C. Lee:** Writing – review & editing, Validation, Methodology, Formal analysis, Conceptualization. **Louise Marston:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Alan Carson:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Mark J. Edwards:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Laura H. Goldstein:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Rachael Maree Hunter:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Kate Holt:** Writing – review & editing, Investigation, Conceptualization. **Jon Marsden:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Markus Reuber:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Jon Stone:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Irwin Nazareth:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

GN, LM & IN receive research funding from the NIHR. MJE does medical expert reporting in personal injury and clinical negligence cases, including in cases of functional neurological disorder (FND). MJE has shares in Brain & Mind, which provides neuropsychiatric and neurological rehabilitation in the independent medical sector, including in people with functional neurological disorder. MJE has received financial support for lectures from the International Parkinson's and Movement Disorders Society and the FND Society (FNDS). MJE receives royalties from Oxford University Press for his book The Oxford Specialist Handbook of Parkinson's Disease and Other Movement Disorder. M.J.E has received honoraria for medical advice to Teva Pharmaceuticals. MJE receives grant funding, including for studies related to FND, from the National Institute for Health and Care Research (NIHR) and the Medical Research Council (MRC). MJE is an associate editor of the European Journal of Neurology. MJE is a member of the international executive committee of the International Parkinson's and Movement Disorders Society and a board member of the FNDS. MJE is on the medical advisory boards of the charities FND Hope UK and Dystonia UK. MR receives a salary from Elsevier as Editor-in-Chief of Seizure – European Journal of Epilepsy, honoraria from UptoDate, and payments from IqVIA for his role on a data management board. He has received speakers fees from UCB Pharma, Jazz Pharma and Angellini and an unrestricted research grant from UCP Pharma. He receives royalties from Oxford University Press and JKP for books on seizures and FND-related subjects. JS reports honoraria from UptoDate, personal fees from Expert Witness Work and grants from National Research Scotland. He runs a free self-help website, www.neurosymptoms.org, for patients with Functional Neurological Disorder. He is secretary of the FND Society and on the medical advisory boards of the charities FND Hope UK and FND Action. AC gives expert testimony in court on a range of neuropsychiatric topics, including FND. He is Past-President of the FND Society and Associate Editor of JNNP. JM has undertaken commercial research for Roche-Hoffmann Pharmaceuticals. All other authors declare no competing interests.

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Data availability

Deidentified participant data can be made available by request to the corresponding author. Requests will be considered after planned analyses and reporting have been completed by the investigators. Access will require submission of a protocol that is approved by a review committee and a signed data access agreement.

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