# Specialist physiotherapy for functional motor disorder in England and Scotland (Physio4FMD): a pragmatic, multicentre, phase 3 randomised controlled trial

# Specialist physiotherapy for functional motor disorder (Physio4FMD): A pragmatic, multicentre, phase 3 randomised controlled trial

Glenn Nielsen, Jon Stone, Teresa C Lee, Laura H Goldstein, Louise Marston, Rachael Maree Hunter, Alan Carson, Kate Holt, Jon Marsden, Marie Le Novere, Irwin Nazareth, Hayley Noble, Markus Reuber, Ann-Marie Strudwick, Beatriz Santana Suarez, Mark J Edwards, on behalf of the Physio4FMD study group.

| | Preferred Degree | Affiliation & Full Address |
|---|---|---|
| Glenn Nielsen | PhD | Neuroscience Research Centre, Institute of Molecular and Clinical Sciences, St. George's University of London, London SW17 0RE, UK |
| Professor Jon Stone | PhD | Centre for Clinical Brain Sciences, Royal Infirmary of Edinburgh, Edinburgh EH16 4SB |
| Teresa C Lee | MSc | Department of Primary Care and Population Health, University College London, London, NW3 2PF, PRIMENT Clinical Trials Unit, University College London, London, NW3 2PF and Department of Statistical Science, University College London, London, WC1E 7HB |
| Professor Laura H Goldstein | PhD | King's College London, Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, London SE5 8AF, UK |
| Professor Louise Marston | PhD | Department of Primary Care and Population Health, University College London, London, NW3 2PF and PRIMENT Clinical Trials Unit, University College London, London, NW3 2PF |
| Professor Rachael Maree Hunter | MSc | Department of Applied Health Research, University College London, London, and PRIMENT Clinical Trials Unit, University College London, London, NW3 2PF |
| Professor Alan Carson | MD | Centre for Clinical Brain Sciences, Royal Infirmary of Edinburgh, Edinburgh EH16 4SB |
| Kate Holt | BSC | Neuroscience Research Centre, Institute of Molecular and Clinical Sciences, St. George's University of London, London SW17 0RE, UK |
| Marie Le Novere | MSc | Department of Applied Health Research, University College London, London, and PRIMENT Clinical Trials Unit, University College London, London, NW3 2PF |
| Professor Jon Marsden | PhD | School of Health Professions, Faculty of Health, University of Plymouth |
| Professor Irwin Nazareth | PhD | Department of Primary Care and Population Health, University College London, London, NW3 2PF and PRIMENT Clinical Trials Unit, University College London, London, NW3 2PF |
| Hayley Noble | MMedSci | Neuroscience Research Centre, Institute of Molecular and Clinical Sciences, St. George's University of London, London SW17 0RE, UK |
| Professor Markus Reuber | PhD | Academic Neurology Unit, University of Sheffield, Royal Hallamshire, Glossop Road, Sheffield, S10 2JF |
| Ann-Marie Strudwick | MSc | Neuroscience, Research and Innovation, King's College Hospital, 245a Coldharbour Lane, London SW9 8RR |
| Beatriz Santana Suarez | BSc | Neuroscience Research Centre, Institute of Molecular and Clinical Sciences, St. George's University of London, London SW17 0RE, UK |
| Professor Mark J Edwards | PhD | Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, London SE5 |

| | | |
|---|---|---|
| | | 8AF, UK & Department of Neuropsychiatry, Maudsley Hospital, London, UK |
| Physio4FMD Author Group | | |

**Corresponding author:** Dr Glenn Nielsen
Neuroscience Research Centre
Institute of Molecular and Clinical Sciences
St Georges University of London
London
SW17 0RE
gnielsen@sgul.ac.uk
Tel: 0208 266 6858

**Orcid ID and email**



| | | Orcid ID |
|---|---|---|
| Dr Glenn Nielsen | gnielsen@sgul.ac.uk | 0000-0001-6053-5670 |
| Prof Jon Stone | jon.stone@ed.ac.uk | 0000-0001-9829-8092 |
| Teresa C Lee | teresa.lee@ucl.ac.uk | 0009-0009-0917-860X |
| Prof Laura H Goldstein | laura.goldstein@kcl.ac.uk | 0000-0001-9387-3035 |
| Prof Louise Marston | l.marston@ucl.ac.uk | 0000-0002-9973-1131 |
| Prof Rachael Maree Hunter | r.hunter@ucl.ac.uk | 0000-0002-7447-8934 |
| Prof Alan Carson | alan.carson@nhslothian.scot.nhs.uk | 0000-0002-7425-0964 |
| Kate Holt | kholt@sgul.ac.uk | 0009-0003-9529-2420 |
| Prof Jon Marsden | jonathan.marsden@plymouth.ac.uk | 0000-0002-2037-4902 |
| Marie Le Novere | marielenovere@outlook.com | 0000-0002-9479-8599 |
| Prof Irwin Nazareth | i.nazareth@ucl.ac.uk | 0000-0003-2146-9628 |
| Hayley Noble | hayley.noble@icnarc.org | 0000-0002-4267-1609 |
| Prof Markus Reuber | m.reuber@sheffield.ac.uk | 0000-0002-4104-6705 |
| Ann-Marie Strudwick | a.strudwick1@nhs.net | 0000-0003-2817-5219 |
| Beatriz Santana Suarez | beatriz.santanasuarez@nhs.net | 0000-0002-1902-8332 |
| Prof Mark J Edwards | mark.j.edwards@kcl.ac.uk | 0000-0002-8283-9015 |



Word count for text: 4441
Number of tables: 3
Number of figures: 3
Number of references: 38

# ABSTRACT

**Background:** Functional motor disorder (FMD), the motor variant of functional neurological disorder, is a disabling condition, commonly associated with poor health outcomes. Recent pathophysiological models have inspired new treatment approaches, including the promising emergence of specialist physiotherapy, although evidence from large randomised controlled trials is lacking. We aimed to assess the clinical effectiveness of a specialist physiotherapy intervention for FMD compared to treatment as usual.

**Methods:** Physio4FMD was a pragmatic, parallel arm, randomised controlled trial. Participants were adults with a "clinically definite" diagnosis of FMD, diagnosed by a neurologist. Recruitment occurred at 11 hospitals in England and Scotland. Participants were randomised (1:1, stratified by site) using a remote web-based application, to receive specialist physiotherapy (a 9-session plus follow-up protocolised intervention), or treatment as usual (referred to local community neurological physiotherapy). Data collection and analysis was blind to treatment allocation. The primary outcome was the Physical Functioning domain of the Short Form 36 (SF36) questionnaire at 12-months post randomisation. Secondary outcomes were a participant rated Clinical Global Impression Scale of Improvement, SF36 health related quality of life, Revised Illness Perception Questionnaire (IPQ-R), Functional Mobility Scale, Hospital Anxiety and Depression Scale (HADS), fatigue 5-point scale, NHS digital data for health service use, and confidence in the correctness of the diagnosis. Analysis followed a modified intention to treat principle, using a complete case approach. Participants who were unable to receive their randomised treatment due to the suspension of healthcare services during the coronavirus pandemic were excluded from the primary analysis. Sensitivity analyses explored the impact of COVID-19 mitigating strategies. The trial is registered with the International Standard Randomised Controlled Trial registry, ISRCTN56136713.

**Findings:** Recruitment commenced 19 October 2018 and concluded 31 January 2022, with a 17-month break during the COVID-19 pandemic. We randomised 179 participants to specialist physiotherapy and 176 to treatment as usual. Eighty-nine participants were excluded due to COVID-19 interruption to treatment (n=27 specialist physiotherapy, n=62 treatment as usual). The primary outcome included data from 241 participants (n=138 [91%] specialist physiotherapy, n=103 [90%] treatment as usual). The primary outcome did not differ significantly between the groups; specialist physiotherapy 37.1 (SD 28.4) vs treatment as usual 37.2 (SD 28.5), adjusted mean difference 3·5 (95% CI -2·3 to 9·3; p=0·23). Some secondary outcomes were significantly different in favour of specialist physiotherapy, and no outcomes

significantly favoured treatment as usual. There were no serious adverse events related to specialist physiotherapy.

**Interpretation:** Specialist physiotherapy resulted in more participants rating their motor symptoms as having improved, and better scores on measures for mental health, but it did not result in better self-reported physical functioning at 12-months. Both specialist and non-specialist physiotherapy appeared to be a safe and valued treatment for selected patients with FMD. Future research should continue to refine interventions for people with FMD and develop evidence-based methods to guide treatment triage decisions.

**Funding:** National Institute for Health and Care Research (NIHR), Health Technology Assessment Programme (project reference 16/31/63).

# INTRODUCTION

Functional neurological disorder (FND) is a common presentation in neurological services.[1] Currently there is consensus that it can be diagnosed accurately, is disabling, and often has a poor outcome if left untreated.[2–4] Treatment is most often thought of in terms of psychotherapeutic input but recently physical rehabilitation has emerged as a promising intervention for the motor symptoms of FND.[5] Contemporary approaches to 'rule in' the FND diagnosis relies on clinical features such as Hoover's sign for functional weakness that highlight differences between impaired voluntary movement and preserved automatic movement.[6] This, along with new aetiological models has opened up more FND specific targets for specialist physiotherapy interventions.

We developed a specialist physiotherapy protocol for the motor symptoms of FND, which we refer to here as functional motor disorder (FMD). The intervention is informed by a Bayesian model of FND,[7] and targets expectations, as well as excessive self-directed attention. Both expectation and attention are presumed to be key mechanisms driving symptoms.[8] The protocol builds on expert consensus recommendations for physiotherapy for FMD.[9] It was tested with promising outcomes in a prospective cohort study and we further developed and tested the intervention in a randomised feasibility study.[10,11] In the feasibility study, 60 people with FMD were randomised to the specialist physiotherapy protocol, comprising 9 sessions conducted over 5 consecutive days, or treatment as usual (TAU), defined as a referral to community neurological physiotherapy. At six-months' follow-up, 72% of the participants in the specialist physiotherapy group rated their symptoms as improved on a 5-point scale, compared to 18% receiving TAU. A range of physical outcome measures showed a moderate to large difference in favour of specialist physiotherapy.

Here we report the main trial, Physio4FMD, based on the feasibility study. The primary aim was to determine the clinical effectiveness of specialist physiotherapy compared to TAU (community neurological physiotherapy) for people with FMD at 12 months post randomisation, with a 6-month interim assessment.

# METHODS

### Study Design

We conducted a pragmatic, multi-centre, parallel group randomised controlled trial comparing a specialist physiotherapy programme for FMD to TAU (referral to community neurological physiotherapy). The study was conducted in the National Health Service (NHS) at 11 secondary and

tertiary care hospitals in England and Scotland. Ethics approval was granted by the London-Surrey Borders Research Ethics Committee, reference number 18/LO/0486, 28 March 2018. The trial was registered with the International Standard Randomised Controlled Trial registry, ISRCTN56136713. The study protocol has been published.[12]

**Participants**

The study participants were adults attending outpatient neurology clinics and inpatients who had received a diagnosis of FMD. Eligibility was determined by consultant neurologists collaborating in the trial. The inclusion criteria were: (i) new or returning patients; (ii) a "clinically definite" diagnosis of FMD according to the Gupta and Lang diagnostic classification criteria;[13] (iii) age 18 or over; (iv) diagnostic investigations have come to an end; (v) the patient is accepting of the intervention; and (vi) the motor symptoms caused significant distress or impairment in social, occupational or other important areas of functioning (subjectively described by the patient) and independent of other comorbidities. The exclusion criteria were: (i) the recruiting neurologist deems the patient to have severe psychiatric comorbidity which would interfere with the patient's ability to participate in physiotherapy; (ii) the patient has another diagnosis which explains the majority of their symptoms or disability; (iii) the patient has pain, fatigue or dissociative seizures that would interfere with their ability to engage with physiotherapy; (iv) disability to the extent that the patient requires assistance for toileting; (v) the patient is unable to attend 9 sessions of physiotherapy over a 3-week period, within 6 weeks of their initial neurology consultation; (vi) ongoing unresolved compensation claim or litigation; (vii) the patient has no fixed address or is seeking rehousing through their council for disability access reasons; (viii) unable to understand English sufficiently to complete questionnaires; (ix) the patient has a documented learning disability that prevents them from answering questionnaires independently; and (x) the patient lacks capacity to give consent. Eligibility was ultimately a clinical decision made by the neurologist, rather than by cut-off scores from standardised assessment tools. Patients were not excluded based on having pain, fatigue, dissociative seizures, anxiety and/or depression. These symptoms were only considered as exclusionary if they were deemed to be severe enough to interfere with the patients' ability to engage with the physiotherapy intervention. All participants gave written informed consent to participate.

**Randomisation and masking**

After completing baseline assessment, participants were randomised (1:1) to specialist physiotherapy or TAU by the trial manager at St George's University of London. Randomisation was conducted using a web-based application created by an independent company, "Sealed Envelope".[14] Block randomisation

with random block sizes was used to ensure even allocation between randomised groups, stratified by site. The randomisation sequence was computer generated and programmed by an independent statistician. Researchers collecting the trial outcomes, statisticians and health economists were masked to treatment allocation, and participants were asked not to reveal their group allocation to research workers. Due to the nature of the intervention, it was not possible to mask the trial manager, participants or treating clinicians.

**Procedures**

*Both groups: the role of the neurologist*

Prior to enrolment in the trial, the diagnosis of FMD was made by a neurologist based on best practice recommendations,[3] and a follow-up consultation was booked within 12 months of the initial consultation. Patients meeting the eligibility criteria were asked for their consent to be contacted about the study by a research worker. During a face-to-face appointment with a member of the research team, a second eligibility screening was conducted, informed consent obtained, and baseline assessments were completed before randomisation. The study neurologists received training from authors ME, JS, or GN. See the appendix for training details (pp 4) and for the participant information sheet and consent form (pp 8).

*Specialist physiotherapy*

The intervention was a protocolised physiotherapy programme which could be adapted to the needs of individuals. The programme consisted of 9 sessions delivered within a three-week period, plus a single follow-up session after three months. The intervention had three broad aims; (i) to help patients understand their symptoms; (ii) to retrain movement with redirection of attention; and (iii) to develop self-management skills. Physiotherapy sessions were guided by an interactive workbook,[15] which formed part of the self-management plan. The treatment has been described in more detail elsewhere.[9–12] The physiotherapists delivering the intervention were specialised in neurorehabilitation. Prior to the trial, all had completed a 5-day training programme supported by an intervention manual.[16] See the appendix for a description of the training (pp 16).

*Treatment as usual (TAU): (community neurological physiotherapy)*

The comparator condition was TAU, defined as a referral made by the diagnosing neurologist to the NHS community neurological physiotherapy service. A referral letter was sent with the neurology consultation letter, which stated the diagnosis of FMD and that the patient may benefit from physiotherapy. As there is no formal pathway or guideline for FMD treatment in the NHS, we were aware that the treatment received by this group would be of mixed quality. Due to the pragmatic

nature of the trial, we were unable to control whether physiotherapy was received or how many sessions were offered to those allocated to this group.

*Follow-up (both groups)*

Follow-up assessments were conducted remotely at six- and 12-months via the participants' preferred method; either an online form, return-mail paper forms, or by telephone. A fidelity and satisfaction with treatment telephone questionnaire was conducted by the trial manager or a designated (unblinded) research worker, between six- and 12-months post randomisation.

**Outcomes**

The primary outcome was the Physical Functioning domain of the SF36 at 12-months post randomisation.[17] The Physical Functioning domain includes 10 questions, rating the level of limitation when attempting vigorous activities, moderate activities, lifting and carrying, mobilising, washing and dressing. The maximum score of 100 indicates optimal physical function.

The secondary measures of clinical effectiveness were a participant-rated Clinical Global Impression of Improvement (CGI-I) (5-point Likert scale,[18] see appendix pp 17), the remaining seven domains of the SF36,[19] the Functional Mobility Scale (FMS),[20] the Revised Illness Perception Questionnaire (IPQ-R),[21] the Hospital Anxiety and Depression Scale (HADS),[22] a measure of Fatigue (5-point scale, see appendix pp 18),[23] Confidence in correctness of the diagnosis of FMD (10-point scale, see appendix pp 19),[24] and healthcare use (digital data held by NHS England and NHS Scotland on hospital-based appointments and admissions).[25,26] The Extended Patient Health Questionnaire was completed at baseline only for secondary exploratory analysis purposes (see appendix pp 20).[27,28] All other outcome measures were collected and analysed at six- and 12-months. Safety and adverse event data were collected as part of self-report six- and 12-month questionnaires, during the assessment of fidelity telephone call, and in follow-up clinical appointments.[29] A health economic analysis was also conducted and will be reported separately.

**Statistical analysis**

The target sample size was calculated using the ANCOVA method to detect a nine-point difference in the SF36 Physical Functioning with 90% power at the 5% level of significance.[12] Assuming a standard deviation of 22 and inflating the sample by a factor of 1·4 to account for therapist effect, we calculated that a minimum of 105 participants were needed per group. The target sample size was inflated by 20% to account for dropouts, giving a sample size of 132 per group. Additional participants were recruited in

an extension of the trial to mitigate the impact of the COVID-19 pandemic. Our COVID-19 mitigation strategies were based on published guidance,[30–32] further details are available in the published analysis plans and appendix (pp 21).[33] The analysis plan was prespecified and published prior to database lock.[33] It details the mitigation strategies and corresponding sensitivity analyses to explore the impact of these decisions.[33] Data were analysed following a modified intention to treat principle, utilising a complete case approach.

The primary outcome was analysed using linear mixed effects modelling, with the physiotherapist and clusters of 1 in the TAU group as the random effect, controlling for baseline values and adjusting for site. Secondary outcomes with continuous scales were analysed using linear mixed models, adjusting for baseline. The CGI-I was dichotomised into (i) Much improved or Improved; and (ii) No change, Worse, or Much worse. The 5-point fatigue scale was similarly dichotomised into (i) no fatigue or slight fatigue; and (ii) moderate, severe, or extreme fatigue. The dichotomised scores were analysed using mixed effects logistic regression, adjusting for baseline values for fatigue and site using fixed effects (site was removed from the model for the 5-point fatigue scale due to insufficient degrees of freedom). Digital hospital episode statistics were analysed using mixed effects negative binomial regression. Proportions, means and standard deviations are reported for self-reported health care usage. We did not adjust for multiple testing. We conducted pre-specified sensitivity analyses to explore the impact of COVID-19 on the trial, the impact of our COVID-19 mitigation strategies, and a dose response analysis (see published analysis plans and appendix pp 21 for further details).[33] We explored compliance with the intervention, which was defined as attending five or more sessions of specialist physiotherapy.[33]

In a post hoc analysis, we looked at the number of participants that made a clinically significant improvement in the primary outcome. The minimum clinically important difference for the SF36 has been found to differ by population studied and this value has not been established in FMD.[34] We therefore chose a conservative value of 10 points based on other conditions.[34]

Analyses were conducted using STATA version 18. The conduct of the trial was monitored by an independent Trial Steering Committee (which included expert clinicians, a statistician, health economist and patient representatives), and an independent Data Monitoring and Ethics Committee.

**Role of the funding source**

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

# RESULTS

Recruitment occurred over 24 months in two blocks, 19 October 2018 – 11 March 2020 and 3 August 2021 – 31 January 2022, with a 17-month break during the COVID-19 pandemic. A total of 355 participants were randomised to specialist physiotherapy (n=179) or TAU (n=176). Due to the nature of the recruitment method, we were unable to collect data on the number screened for inclusion.

Participants were categorised into four groups based on their interaction with the COVID-19 pandemic. Group A (n=25) completed follow-up before 23 March 2020 (when national COVID-19 lockdown was instigated in the UK). Group B (n=134) completed treatment before 23 March 2020, but completed follow-up after 23 March 2020. Group C (n=89) were randomised but did not receive treatment prior to 23 March 2020, and completed follow-up after 23 March 2020. Group D (n=88) were recruited in the extension after 3 August 2021. The 19 participants unaccounted for in these groups were lost to follow-up at the time groups were determined and their treatment status could not be established. An additional 6 participants were subsequently lost to follow-up (Figure 1). Participants in Group C were excluded from the primary analysis,[33] on the basis that the COVID-19 lockdowns prevented them from receiving their allocated treatment. The TAU group was more frequently represented in Group C due to longer waits to start physiotherapy (n=27 specialist physiotherapy, n=62 TAU).

The primary analysis (Groups A, B and D) included 247 participants (n=141 specialist physiotherapy, n=106 TAU). Data on the primary outcome were obtained for 138 (91%) participants in specialist physiotherapy, and 103 (90%) participants in TAU. All randomised participants (Groups A – D) with follow-up data were included in the sensitivity analyses, n=314 participants (158 intervention, 157 control) with 88% retention for the primary outcome.

Baseline characteristics are reported for Groups A, B and D (Table 1). Baseline data for Group C are reported in the appendix (pp 23). The mean age of participants was 44·7 (SD 14·6), 74% were female and the mean symptom duration was 4·8 (SD 6·3) years (median 2.6, IQR 1.2 – 5.6). Participant-reported past medical history is reported in the appendix (pp 25).

The median time between randomisation and commencing treatment for specialist physiotherapy was 36 days (IQR 24·8–57·8) and for TAU 97 days (IQR 60·2–176·2). The median duration of treatment (days between first and final treatment session) was 15 days for specialist physiotherapy (IQR 10·0–21·5) and 93 days (IQR 47–148·5) for TAU. The median time between completing treatment and completing the primary (12-month) outcome was 310 days (IQR 281·5–323) for specialist physiotherapy and 179 days

(IQR 123–237·5) for TAU. The median number of treatment sessions completed in the specialist physiotherapy group was 9 (IQR 8–9) and 4 (IQR 2–7) in TAU. See appendix for details of the timing (pp 30) and contents (pp 36) of treatment for both randomised groups.

Demographic characteristics of the physiotherapists delivering specialist physiotherapy, assessment of fidelity, and satisfaction with treatment data are presented in the appendix (pp 31–41). In summary, the data suggested high ratings of intervention fidelity. Compared to TAU, participants receiving specialist physiotherapy were more satisfied with their physiotherapists (100% were completely satisfied or satisfied vs 77·3%); more satisfied with their treatment (96·7% were completely satisfied or satisfied vs 65·3%); and rated their physiotherapists as having a greater understanding of their movement problem (median score out of 10 was 10 vs 8).

The primary and secondary outcomes at 12-months are shown in Table 2. The primary outcome, the SF36 Physical Functioning domain, did not differ between treatment arms at 12-months (adjusted mean difference 3·5, 95% CI -2·3 to 9·3, p=0·232).

In secondary outcomes at 12-months, the CGI-I showed a difference in favour of specialist physiotherapy; 58·7% rated their symptoms as “much improved” or “improved”, compared to 38·2% of TAU (odds ratio [OR] 2·3, 95% CI 1·4 to 3·9). The Mental Health domain was significantly better for specialist physiotherapy (adjusted mean difference 5·4, 95% CI 0·9 to 9·8), and there were no significant differences for the remaining SF36 domains (Physical Role, Bodily Pain, General Health, Energy/Vitality, Social Functioning, and Emotional Role). Confidence in the diagnosis was greater for specialist physiotherapy (adjusted mean difference 0·8, 95% CI 0·2 to 1·4). For the IPQ-R, two items were significantly different in favour of specialist physiotherapy (Personal Control and Illness Coherence) and there were no significant differences for the remaining items (Identity, Causes, Timeline, Timeline cyclical, Consequences, Treatment control, and Emotional representation). No differences between groups were found for the remaining secondary outcomes (Functional Mobility Scale, HADS Anxiety or Depression, Fatigue 5-point scale, and health care use). Treatment as usual was not favoured in any outcome. Figure 2 shows the standardised effect sizes at six and 12-months. See the appendix (pp 42-50) for figures and tables of all outcomes, including digital health care data (pp 46), and outcomes for outcomes at six-months post randomisation (pp 47).

We found that 92·2% were compliant with the specialist physiotherapy intervention (defined as attending five or more sessions). Sensitivity analyses revealed that including Group C in the analysis had no impact on the significance of the primary outcome. When analysing data from all randomised

participants, the adjusted mean difference between groups was 4·3, favouring specialised therapy (95% CI -0·8 to 9·4). The primary and secondary outcomes for Group C and further details are reported in the appendix (pp 51–55). The dose-response analysis suggested that attending more sessions is associated with better scores for the primary outcome. However, due to the high compliance this finding is a relative one with only nine participants having attended less than eight sessions. Due to high levels of compliance and low levels of missing data, the pre-planned analyses to explore the effect of compliance and missing data were not required.

Adverse events and serious adverse events are reported in Table 3. In total, 59 serious adverse events were reported by groups A, B and D. One event resulted in death, which was death by suicide of a participant receiving specialist physiotherapy. The medical notes for this case were recalled, examined, and it was concluded that a possible relationship was unlikely as there were other clear risk factors directly associated with the event. All events were classified as unrelated to treatment, although possible relationships cannot be completely ruled out. See appendix for additional details (pp 58-61). We investigated any event that potentially indicated a new neurological diagnosis, or an incorrect original diagnosis of FMD. Details are available in the appendix (pp 62). One case of diagnostic error was identified, resulting in a misdiagnosis rate of 0·3% at 12 months.

In post hoc analysis, we looked at the number of participants that made a clinically significant improvement in the primary outcome. In the specialist physiotherapy group, 67 (48·6%) reported a 10-point improvement, compared to 39 (38·2%) in TAU.

**Figure 1. Trial Profile**

**Table 1. Baseline Characteristics (Groups A, B and D)**

Footnotes:

a indicates variables with missing data, so the denominator is less than 141 for specialist physiotherapy or 106 for treatment as usual.

B Multiple sites/body parts could be affected.

**Table 2. Primary and secondary outcomes (Groups A, B and D)**

Footnotes:

*Denotes a statistically significant difference.

a Intraclass correlation coefficient (ICC) for specialist physiotherapy group=0·095 (95% CI 0·000 to 0·247)

b Odds ratio of improving if assigned to specialist physiotherapy (much improved or improved vs no change, worse, or much worse).

C Functional Mobility Scale rates the assistance needed over three distances: 5 metres, 50 metres, 500 metres. Each distance is rated from 1-6: 1=uses wheelchair; 2=uses walker/frame; 3=uses crutches; 4=uses walking stick(s); 5=independent but needs to hold rail on stairs; 6=independent on all surfaces.

D HADS Anxiety and Depression cut-off score of 8+ has been found to have acceptable sensitivity and specificity for cases of anxiety and depression (Bjelland et al 2002)

e Odds ratio of milder fatigue if assigned to specialist physiotherapy (no or slight fatigue vs moderate, severe, or extreme).

Reference: Bjelland, I., Dahl, A. A., Haug, T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale An updated literature review. Journal of Psychosomatic Research, 52, 69–77.

**Table 3. Adverse and serious adverse events**

Footnotes:

[a] COVID Group X, were those who were unassigned to a COVID group as they were lost to follow-up at the time the COVID groups were assigned, or they had withdrawn from the study.

[b] Adverse events were defined as any untoward medical occurrence, regardless of causal relationship with treatment, and not meeting the criteria for a serious adverse event.

[c] Serious adverse events were defined as any untoward occurrence that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect, or was otherwise considered medically significant by the investigator. No serious adverse events were deemed to be related to receiving physiotherapy.

**Figure 2. Continuous outcome measures, effect size (ES) and 95% confidence interval (CI) at six and 12-months, adjusting for baseline values and sites and standardising by baseline values of each outcome due to differences in scale.**

Footnotes:

Abbreviations: SP=specialist physiotherapy; TAU=treatment as usual; N=maximum number of participants; n=number of participants with available data.

**Figure 3. Participant rated Clinical Global Impression scale of Improvement at six- and 12-months.**

Legend: Participant rated perception of improvement, in answer to the question, “After physiotherapy, the problem with my movement is…” Odds ratio of improvement at 6-months for specialist physiotherapy compared treatment as usual was 4·7 (95% CI 2·6 to 8·6); odds ratio at 12-months 2·3 (1·4 to 3·9).

# DISCUSSION

This is the first powered, randomised controlled trial of physical rehabilitation for FMD. Although treatment groups did not differ for the primary outcome, the specialist physiotherapy group were twice as likely to report an improvement in their motor symptoms at 12-months. Additionally, specialist physiotherapy led to higher scores for SF36 Mental Health at 12-months. The specialist physiotherapy group had more confidence that their diagnosis was correct, and higher scores of IPQ-R items relating to self-efficacy. With the caveat that participants were screened for their suitability for physiotherapy by expert neurologists, physiotherapy proved to be safe with no serious adverse events related to treatment.

In the specialist physiotherapy group, 59% rated their motor symptoms as improved, and 49% recorded a 10-point improvement in the SF36 Physical Functioning score from baseline. In TAU, 38% rated their motor symptoms as improved and 38% had 10-point improvement in SF36 Physical Functioning. The heightened perception of improvement compared to physical functioning score in specialist physiotherapy may be simply a consequence of improved motor functioning but could also be explained in part through the findings of improved understanding of symptoms, greater perception of control over symptoms, greater confidence in the correctness of the diagnosis, and greater SF36 Mental Health scores. Altogether these changes are likely to reflect greater self-efficacy and a reduced threat value of symptoms leading to a greater perception of improvement.

Outcome measurement is notoriously difficult in FMD, with challenges including symptom heterogeneity, variability of symptom severity, and multifactorial causes of disability and distress.[35] These factors impact the validity of assessment tools and their sensitivity to change. The disparity between the SF36 Physical functioning and CGI-I raises questions about their relative value as an outcome measure. A recent consensus recommendation for a core outcome measure set for FND recommended the CGI-I as the most useful measure, due to its relative resistance to symptom variability and heterogeneity.[36] With this measure we found a difference between treatment groups in favour of specialist physiotherapy. There is an absence of validated objective outcome measures for FMD.[36] Measures such as the Simplified Functional Movement Disorders Rating Scale,[37] rely on the subjective assessment of a third-party observer and so are not truly objective. Although this measure would have added a valuable dimension of data to our study, its use was beyond the practical limits of this pragmatic trial. In lieu of other practicable objective measures, we included digital health use data as a proxy measure of change, with which we did not find any significant differences.

The results for the primary outcome differ from the preceding feasibility study, which showed a moderate to large treatment effect size at six-months for SF36 Physical Functioning.[11] However, the CGI-I outcomes are more closely aligned. In the current study, improvement at six-months was reported in 63% of specialist physiotherapy and 28% of TAU participants. In the feasibility study these values were 72% and 18%. The improved performance of TAU in the current study is notable and may in part explain the lack of difference between randomised groups. It is possible that the quality of community physiotherapy has improved in the five years since the feasibility study, related to increased awareness, published clinical resources for physiotherapists, international conferences, and the founding of an international society.[6] This is supported by data from the feasibility interview which shows that most participants in TAU received treatments that were in line with consensus recommendations.[9] The improved scores in both groups from baseline to 12-months also supports this argument; although some of this improvement could be explained by regression towards the mean.

Other factors that may account for differences from the feasibility study include the greater complexity of participants in this trial at baseline as indicated by worse physical and mental health scores. The intervention was delivered more intensively in the feasibility study (over five consecutive days), which may be associated with greater effectiveness. Differences in therapist skill and practice in delivering the intervention across the two studies might have affected the efficacy of the intervention.

The only other published randomised trial of rehabilitation for FMD compared three-weeks of inpatient multidisciplinary treatment for functional gait disorder to a waiting list control (no treatment).[38] The study found an immediate treatment effect of 8·4 units of the Functional Mobility Scale and 11·7 units of the Short Form 12 (SF12) Physical score, which was maintained and slightly improved at 12-months follow-up (14·1 units). Direct comparisons to this study are limited by differences in study design and the patient cohort (gait disorder vs mixed motor symptoms, and symptom duration 9·5 months vs 4·8 years). Both studies report similar levels of improvement from baseline to 12-months, assuming that SF36 Physical Functioning domain and SF12 Physical score are comparable.

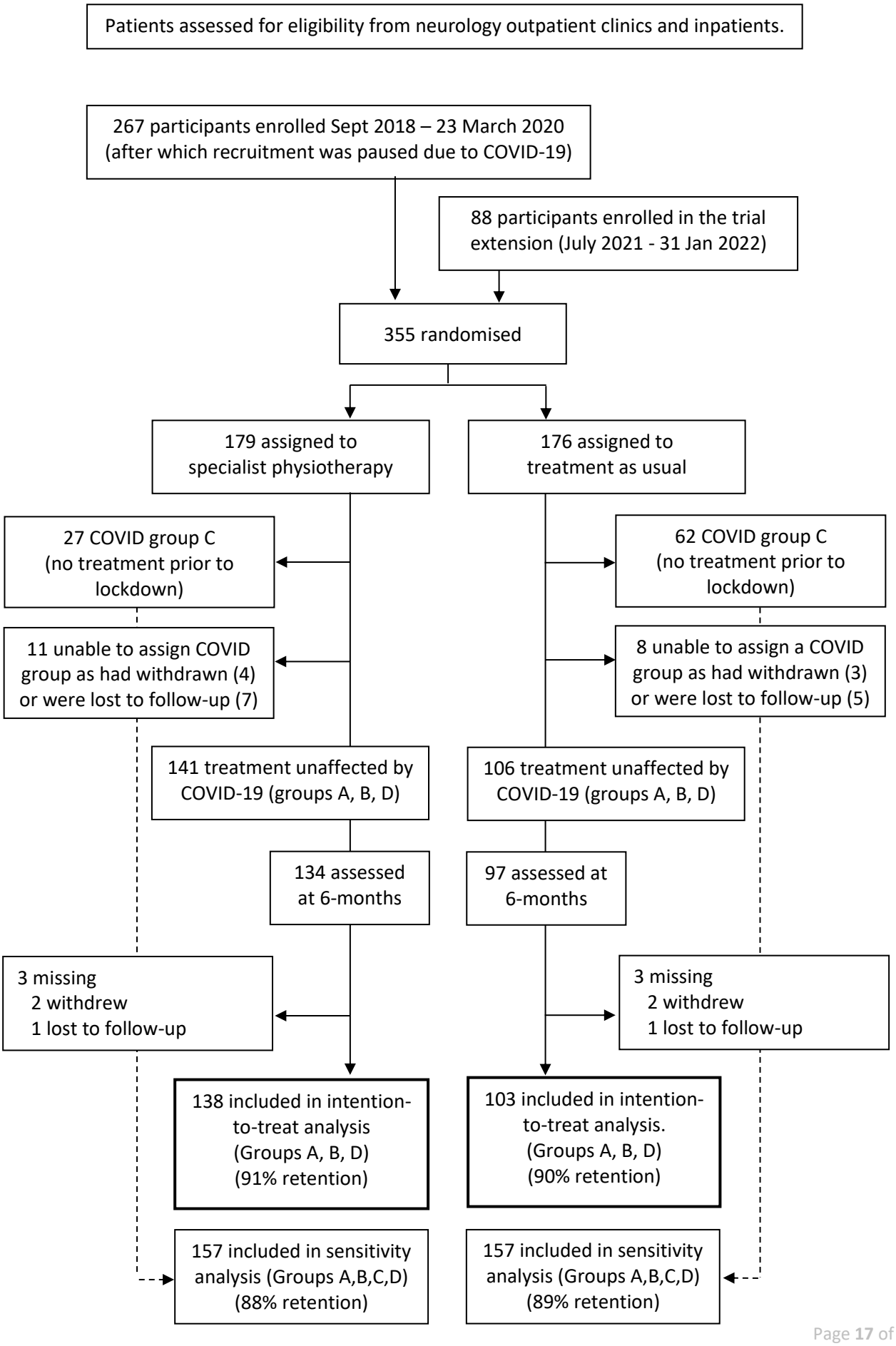
We acknowledge our study has limitations. By chance, randomisation may have disadvantaged the specialist physiotherapy group, which had a slightly longer mean symptom duration, and the higher rates of previous physiotherapy and occupational therapy may have meant these individuals benefited less from additional treatment. Conversely, the lower mean number of treatment sessions in TAU and lower satisfaction with treatment is likely to have worked in favour of specialist physiotherapy. With a large number of secondary outcomes, significance may have occurred by chance, and we did not correct for multiple comparisons. However, 14 out of 54 comparisons (26%) were significantly different in

favour of specialist physiotherapy and this is a greater number than would be expected by chance alone. Most of our outcome measures were participant reported. We designed a pragmatic trial with a real-world comparator. We therefore did not attempt to control the treatment received by this group. The resulting treatment varied in terms of content, quality, duration, and waiting time. Longer waiting times for treatment in TAU meant that these participants had concluded their treatment closer to the 6 and 12-month assessment points, which may have influenced the results (the effect of specialist physiotherapy needed to last longer). Sensitivity analyses did not show significant differences in participants recruited before and after the pandemic for the primary outcome, although it is impossible to rule out potential confounding factors of the treatment interruptions caused by COVID-19 or our mitigating strategies. We cannot rule out placebo and nocebo effects associated with the randomised groups. We attempted to minimise these nonspecific effects in the way we described the trial treatments to potential participants (for more details see neurologist training in the appendix pp 4, and patient information sheet, appendix pp 8). Strengths of our study include the large sample size, a high rate of compliance and retention, follow-up over 12 months, and blinding of those involved with data collection and analysis. Generalisability is supported in that the intervention was carried out at multiple sites, with high fidelity, following training and support with supervision.

Questions for future research include, do interventions delivered earlier in the trajectory of FMD improve outcome? What are the optimal ingredients, duration and intensity for physiotherapy? In view of the heterogeneity of the patient population, research should identify which patients are most likely to benefit from specialist physiotherapy and how to meet the needs of those who are unlikely to benefit. More evidence is needed to guide the addition of multidisciplinary expertise to the rehabilitation of some patients, such as psychological therapy and occupational therapy, as well as considering potential adjuncts to physiotherapy, such as neuromodulation, hypnosis, and non-specific exercise. Finally, research is needed to develop validated subjective and objective outcome measures for FMD.

In conclusion, the specialist physiotherapy protocol for FMD did not result in better self-reported physical functioning compared to (non-FMD specialist) neurological physiotherapy. Both treatment groups showed improved mean Physical Functioning scores over the 12-month study period. However, the specialist physiotherapy group were more likely to rate their motor symptoms as improved. These changes occurred despite baseline assessments revealing long symptom durations and high levels of physical disability, anxiety and depression. Taken together with the very high levels of satisfaction with treatment, specialist physiotherapy appears to be a valued and safe treatment option for a proportion of people with FMD.

## Figure 1. Trial Profile



# Table 1. Baseline Characteristics (Groups A, B and D)

| | Specialist Physiotherapy (n=141) | Treatment as usual (n=106) | Total (n=247) |
|---|---|---|---|
| **Age, years** | | | |
| Mean (SD) | 45·0 (14·3) | 44·4 (14·9) | 44·7 (14·6) |
| Median (IQR) | 48 (33 – 55) | 45 (31 – 55) | 46 (33 – 55) |
| **Gender** | | | |
| Male | 37 (26·2%) | 27 (25·5%) | 64 (25·9%) |
| Female | 104 (73·8%) | 79 (74·5%) | 183 (74·1%) |
| **Ethnicity** | | | |
| White | 126 (89·4%) | 97 (91·5%) | 223 (90·3%) |
| Black | 6 (4·3%) | 1 (0·9%) | 7 (2·8%) |
| Asian | 6 (4·3%) | 2 (1·9%) | 8 (3·2%) |
| Mixed | 2 (1·4%) | 5 (4·7%) | 7 (2·8%) |
| Other | 1 (0·7%) | 1 (0·9%) | 2 (0·8%) |
| **Relationship status and dependents** | | | |
| Married or cohabitating with partner | 72 (54·6%) | 64 (59·4%) | 136 (55·1%) |
| Single, separated, or widowed | 64 (45·4%) | 43 (40·6%) | 107 (43·3%) |
| Has dependents | 52 (36·9%) | 41 (38·7%) | 93 (37·7%) |
| **Care needs** | | | |
| Has a carer | 56 (39·7%) | 27 (25·5%) | 83 (33·6%) |
| Has a paid carer | 17 (12·1%) | 7 (6·6%) | 24 (9·7%) |
| **Highest qualification, years of education** | | | |
| No qualification | 11 (7·8%) | 4 (3·8%) | 15 (6·1%) |
| General Certificate of Secondary Education | 35 (24·8%) | 25 (23·6%) | 60 (24·3%) |
| A level | 25 (17·7%) | 16 (15·1%) | 41 (16·6%) |
| National Vocational Qualification | 26 (18·4%) | 17 (16·0%) | 23 (9·3%) |
| Higher National Certificate/Diploma | 16 (11·4%) | 7 (6·6%) | 45 (18·2%) |
| Degree | 18 (12·8%) | 27 (25·5%) | 45 (18·2%) |
| Higher Degree | 9 (6·4%) | 9 (8·5%) | 18 (7·3%) |
| Other | 1 (0·7%) | 1 (0·9%) | 2 (0·8%) |
| Years of education (SD) | 14·2 (3·8) | 14·4 (2·8) | 14·3 (3·4) |
| **Employment status** | | | |
| Working or studying | 49 (34·8%) | 37 (34·9%) | 86 (34·8%) |
| Not working/studying because of sickness | 40 (28·4%) | 31 (29·3%) | 71 (28·7%) |
| Not working because of unemployment | 42 (29·8%) | 29 (27·4%) | 71 (28·7%) |
| Other | 10 (7·1%) | 9 (8·5%) | 19 (7·7%) |
| **Previous treatment** | | | |
| Physiotherapy | 69 (49·6%)[a] | 42 (40·4%) [a] | 111 (45·7%) [a] |
| Psychology | 25 (18·0%) [a] | 17 (16·4%) [a] | 42 (17·3%) [a] |
| Occupational Therapy | 22 (15·8%) [a] | 8 (7·7%) [a] | 30 (12·3%) [a] |
| Specialist inpatient rehabilitation | 5 (3·7%) [a] | 4 (3·9%) [a] | 9 (3·7%) [a] |
| **Symptom duration, years** | | | |
| Mean (SD) | 5·2 (7·2) | 4·4 (4·9) | 4·8 (6·3) |
| Median (IQR) | 2·6 (1·3 – 6·0) | 2·6 (1·1 – 5·4) | 2·6 (1·2 –5·6) |
| **Dominant motor symptom** | | | |
| Weakness | 47 (33·3%) | 31 (29·2%) | 78 (31·6%) |
| Gait disturbance | 45 (31·9%) | 35 (33·0%) | 80 (32·4%) |
| Tremor | 21 (14·9%) | 13 (12·3%) | 34 (13·8%) |
| Mixed movement disorder | 19 (13·5%) | 16 (15·1%) | 35 (14·2%) |
| Jerks | 7 (5·0%) | 6 (5·7%) | 13 (5·3%) |
| Dystonia / fixed dystonia | 2 (1·4%) | 5 (4·7%) | 7 (2·8%) |
| **Body part affected, dominant hand [b]** | | | |

| | | | |
|---|---|---|---|
| Left upper limb | 68 (48·3%) | 43 (40·6%) | 111 (44·9%) |
| Right upper limb | 68 (48·3%) | 45 (42·5%) | 113 (45·7%) |
| Left lower limb | 99 (70·2%) | 74 (69·8%) | 173 (70·0%) |
| Right lower limb | 92 (65·3%) | 75 (70·8%) | 167 (67·6%) |
| Head/neck | 36 (25·5%) | 20 (18·8%) | 56 (22·7%) |
| Trunk | 31 (22·0%) | 13 (12·3%) | 44 (17·8%) |
| Dominant hand, right | 128 (90·8%) | 97 (91·5%) | 225 (91·1%) |

[a] indicates variables with missing data, so the denominator is less than 141 for specialist physiotherapy or 106 for treatment as usual.

[b] Multiple sites/body parts could be affected.

# Table 2. Primary and secondary outcomes (Groups A, B and D)

| | Specialist physiotherapy n=152 maximum | Treatment as usual n=114 maximum | Difference adjusting for baseline (95% CI) |
|---|---|---|---|
| **SF36 Physical Functioning, mean (SD)** Scale range 0-100 | | | |
| Baseline | 26·3 (23·1) | 30·9 (23·2) | |
| Participants with available data | 141 (93%) | 106 (93%) | |
| 12-months | 37·1 (28·4) | 37·2 (28·5) | 3·534 (-2·258, 9·325)[a] |
| Participants with available data | 138 (91%) | 103 (90%) | |
| **SF36 Physical Role Limitations, mean (SD)** Scale range 0-100 | | | |
| Baseline | 20·9 (21·3) | 21·9 (22·2) | |
| Participants with available data | 141 (93%) | 106 (93%) | |
| 12-months | 33·0 (26·9) | 31·8 (27·0) | 2·267 (-3·687, 8·221) |
| Participants with available data | 138 (91%) | 103 (90%) | |
| **SF36 Bodily Pain, mean (SD)** Scale range 0-100 | | | |
| Baseline | 28·4 (22·7) | 32·6 (23·3) | |
| Participants with available data | 141 (93%) | 106 (93%) | |
| 12-months | 35·4 (26·4) | 37·1 (25·6) | 1·144 (-4·615, 6·902) |
| Participants with available data | 138 (91%) | 103 (90%) | |
| **SF36 General Health Perceptions, mean (SD)** Scale range 0-100 | | | |
| Baseline | 34·2 (19·4) | 37·1 (21·7) | |
| Participants with available data | 141 (93%) | 106 (93%) | |
| 12-months | 34·9 (18·9) | 35·5 (20·9) | 1·796 (-1·977, 5·570) |
| Participants with available data | 136 (89%) | 103 (90%) | |
| **SF36 Energy/Vitality, mean (SD)** Scale range 0-100 | | | |
| Baseline | 22·2 (16·7) | 22·3 (18·0) | |
| Participants with available data | 141 (93%) | 106 (93%) | |
| 12-months | 29·8 (20·3) | 26·1 (18·7) | 3·752 (-0·874, 8·377) |
| Participants with available data | 137 (90%) | 103 (90%) | |
| **SF36 Social Functioning, mean (SD)** Scale range 0-100 | | | |
| Baseline | 29·5 (22·6) | 30·8 (26·5) | |
| Participants with available data | 141 (93%) | 106 (93%) | |
| 12-months | 38·8 (27·7) | 38·1 (27·5) | 1·068 (-5·356, 7·492) |
| Participants with available data | 137 (90%) | 103 (90%) | |
| **SF36 Emotional Role Limitations, mean (SD)** Scale range 0-100 | | | |
| Baseline | 48·7 (34·3) | 50·8 (36·8) | |
| Participants with available data | 141 (93%) | 106 (93%) | |
| 12-months | 51·1 (32·0) | 48·9 (33·5) | 3·638 (-2·850, 10·126) |
| Participants with available data | 138 (91%) | 103 (90%) | |
| **SF36 Mental Health, mean (SD)** Scale range 0-100 | | | |
| Baseline | 52·3 (21·5) | 54·0 (21·7) | |
| Participants with available data | 141 (93%) | 106 (93%) | |
| 12-months | 55·1 (23·3) | 51·4 (23·9) | **5·360 (0·940, 9·779)*** |

| | | | |
|---|---|---|---|
| Participants with available data | 137 (90%) | 103 (90%) | |
| **Participant rated Clinical Global Impression Scale of Improvement (frequency)** | | | |
| **12-month** | | | |
| Participants with available data | 138 (91%) | 102 (89%) | |
| Much Improved | 36 (26·1%) | 14 (13·7%) | |
| Improved | 45 (32·6%) | 25 (24·5%) | |
| No Change | 41 (29·7%) | 47 (46·1%) | |
| Worse | 12 (8·7%) | 10 (9·8%) | |
| Much Worse | 4 (2·9%) | 6 (5·9%) | |
| | | | |
| Good outcome (Much Improved, or Improved) | 81 (58·7%) | 39 (38·2%) | |
| Poor outcome (No Change, Worse, or Much Worse) | 57 (41·3%) | 63 (61·8%) | |
| Odds ratio of improving (95% CI)[b] | | | **2·315 (1·361, 3·938)*** |
| **Functional Mobility Scale, mean (SD)** [c] Scale range 3-18 | | | |
| Baseline | 11·4 (4·5) | 11·5 (4·4) | |
| Participants with available data | 140 (92%) | 104 (91%) | |
| 12-months | 12·2 (4·5) | 11·9 (4·6) | 0·598 (-0·198, 1·395) |
| Participants with available data | 136 (89%) | 97 (85%) | |
| **Hospital Anxiety and Depression Scale: Anxiety, mean (SD)** [d] Scale Range 0-21 | | | |
| Baseline | 10·3 (5·0) | 9·5 (5·2) | |
| Participants with available data | 140 (92%) | 105 (92%) | |
| 12-months | 10·0 (5·2) | 9·4 (4·9) | -0·531 (-1·412, 0·350) |
| Participants with available data | 135 (89%) | 97 (85%) | |
| **Hospital Anxiety and Depression Scale: Depression, mean (SD)** [d] Scale Range 0-21 | | | |
| Baseline | 8·8 (4·1) | 8·3 (4·4) | |
| Participants with available data | 140 (92%) | 105 (92%) | |
| 12-months | 8·5 (4·7) | 8·2 (4·8) | -0·203 (-1·200, 0·795) |
| Participants with available data | 135 (89%) | 97 (85%) | |
| **Fatigue 5-point scale (frequency)** | | | |
| **Baseline** | | | |
| Participants with available data | 141 (93%) | 106 (93%) | |
| No tiredness/fatigue | 3 (2·1%) | 2 (1·9%) | |
| Slight | 12 (8·5%) | 16 (15·1%) | |
| Moderate | 68 (48·2%) | 35 (33·0%) | |
| Severe | 42 (29·8%) | 38 (35·9%) | |
| Extreme | 16 (11·4%) | 15 (14·2%) | |
| | | | |
| No Fatigue or Slight Fatigue | 15 (10·4) | 18 (17·0%) | |
| Moderate, Severe, or Extreme Fatigue | 129 (89·6) | 88 (83·0%) | |
| | | | |
| **12-month** | | | |
| Participants with available data | 136 (89%) | 97 (85%) | |
| No tiredness/fatigue | 5 (3·7%) | 2 (2·1%) | |
| Slight | 18 (13·2%) | 14 (14·4%) | |
| Moderate | 44 (32·4%) | 32 (33·0%) | |
| Severe | 36 (26·5%) | 36 (37·1%) | |
| Extreme | 33 (24·3%) | 13 (13·4%) | |

| | | | |
|---|---|---|---|
| | | | |
| No Fatigue or Slight Fatigue | 23 (16·9%) | 16 (16·5%) | |
| Moderate, Severe, or Extreme Fatigue | 113 (83·1%) | 81 (83·5%) | |
| Odds ratio of milder fatigue (95% CI)[e] | | | 1·102 (0·621, 1·955) |
| **Confidence in the diagnosis, mean (SD)** Scale range 0-10 | | | |
| Baseline | 8·1 (2·0) | 8·0 (2·2) | |
| Participants with available data | 141 (93%) | 106 (93%) | |
| 12-months | 8·1 (2·3) | 7·4 (2·8) | **0·781 (0·193, 1·369)*** |
| Participants with available data | 134 (88%) | 94 (82%) | |
| **Revised Illness Perception Questionnaire, mean (SD)** | | | |
| Scale range 0-14 | | | |
| **Identity** Baseline | 9·0 (2·7) | 8·6 (2·9) | |
| Participants with available data | 139 (91%) | 105 (92%) | |
| **Identity** 12-months | 9·3 (2·7) | 9·1 (3·0) | -0·247 (-0·839, 0·345) |
| Participants with available data | 132 (87%) | 94 (82%) | |
| | | | |
| Scale range 18-90 | | | |
| **Causes** Baseline | 40·8 (10·4) | 40·9 (12·0) | |
| Participants with available data | 139 (91%) | 105 (92%) | |
| **Causes** 12-months | 42·0 (10·2) | 41·7 (10·6) | -0·183 (-2·404, 2·038) |
| Participants with available data | 132 (87%) | 94 (82%) | |
| | | | |
| Scale range 6-30 | | | |
| **Timeline** Baseline | 20·6 (4·4) | 20·3 (4·5) | |
| Participants with available data | 140 (92%) | 106 (93%) | |
| **Timeline** 12-months | 22·8 (4·5) | 22·2 (4·0) | -0·194 (-1·175, 0·787) |
| Participants with available data | 132 (87%) | 94 (82%) | |
| | | | |
| Scale range 4-20 | | | |
| **Timeline cyclical** Baseline | 14·2 (3·7) | 14·0 (3·95) | |
| Participants with available data | 141 (93%) | 106 (93%) | |
| **Timeline cyclical** 12-months | 13·7 (3·7) | 13·7 (3·7) | -0·188 (-1·021, 0·644) |
| Participants with available data | 133 (87%) | 94 (82%) | |
| | | | |
| Scale range 6-30 | | | |
| **Consequences** Baseline | 24·0 (4·0) | 23·9 (3·6) | |
| Participants with available data | 140 (92%) | 105 (92%) | |
| **Consequences** 12-months | 22·6 (4·5) | 22·8 (4·0) | -0·573 (-1·508, 0·362) |
| Participants with available data | 132 (87%) | 94 (82%) | |
| | | | |
| Scale range 6-30 | | | |
| **Personal control** Baseline | 18·6 (4·0) | 19·7 (3·8) | |
| Participants with available data | 140 (92%) | 105 (92%) | |
| **Personal control** 12-months | 19·4 (4·4) | 19·0 (4·2) | **1·108 (0·138, 2·079)** |
| Participants with available data | 133 (87%) | 94 (82%) | |
| | | | |
| Scale range 5-25 | | | |
| **Treatment control** Baseline | 16·3 (2·6) | 16·9 (2·6) | |
| Participants with available data | 140 (92%) | 105 (92%) | |
| **Treatment control** 12-months | 15·7 (3·7) | 15·9 (3·5) | 0·339 (-0·512, 1·190) |
| Participants with available data | 133 (87%) | 94 (82%) | |
| | | | |
| Scale range 5-25 | | | |
| **Illness coherence** Baseline | 13·3 (4·7) | 13·7 (4·7) | |

| | | | |
|---|---|---|---|
| Participants with available data | 141 (93%) | 106 (93%) | |
| **Illness coherence** 12-months | 17·2 (4·9) | 15·6 (5·0) | **1·669 (0·592, 2·745)*** |
| Participants with available data | 133 (87%) | 94 (82%) | |
| | | | |
| Scale range 6-30 | | | |
| **Emotional representation** Baseline | 21·4 (5·3) | 20·4 (5·3) | |
| Participants with available data | 141 (93%) | 106 (93%) | |
| **Emotional representation** 12-months | 19·5 (5·5) | 19·6 (4·7) | -0·911 (-1·999, 0·176) |
| Participants with available data | 133 (87%) | 94 (82%) | |
| | | | |
| Scale range 56-294 | | | |
| **TOTAL** Baseline | 176·0 (16·8) | 175·5 (21·6) | |
| Participants with available data | 133 (87%) | 102 (89%) | |
| **TOTAL** 12-months | 178·0 (17·9) | 176·2 (19·5) | 0·171 (-3·422, 3·764) |
| Participants with available data | 129 (85%) | 94 (82%) | |
| **Extended Patient Health Questionnaire, mean (SD)**<br>Scale range 0-31 | | | |
| Assessed at baseline only | 16·9 (5·7) | 15·7 (5·7) | |
| Participants with available data | 135 (89%) | 105 (92%) | |
| | | | |

*Denotes a statistically significant difference.

[a] Intraclass correlation coefficient (ICC) = 0.017.

[b] Odds ratio of improving if assigned to specialist physiotherapy (much improved or improved vs no change, worse, or much worse).

[c] Functional Mobility Scale rates the assistance needed over three distances: 5 metres, 50 metres, 500 metres. Each distance is rated from 1-6: 1=uses wheelchair; 2=uses walker/frame; 3=uses crutches; 4=uses walking stick(s); 5=independent but needs to hold rail on stairs; 6=independent on all surfaces.

[d] HADS Anxiety and Depression cut-off score of 8+ has been found to have acceptable sensitivity and specificity for cases of anxiety and depression (Bjelland et al 2002)

[e] Odds ratio of milder fatigue if assigned to specialist physiotherapy (no or slight fatigue vs moderate, severe, or extreme).

Reference:

Bjelland, I., Dahl, A. A., Haug, T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale An updated literature review. *Journal of Psychosomatic Research*, *52*, 69–77.

# Table 3. Adverse and Serious Adverse Events

| | COVID Groups A, B and D | | COVID Groups C and X[a] | |
|---|---|---|---|---|
| | **Specialist Physiotherapy n=141** | **Treatment as usual n=106** | **Specialist Physiotherapy n=38** | **Treatment as usual n=70** |
| **Adverse Events[b]** | | | | |
| Participants with at least 1 event | 41 (29·1%) | 26 (24·5%) | 6 (15·8%) | 9 (12·9%) |
| Total number of events | 64 | 32 | 9 | 13 |
| Relationship to treatment | | | | |
| Not related | 56 | 32 | 9 | 13 |
| Possibly | 1 | 0 | 0 | 0 |
| Probably | 6 | 0 | 0 | 0 |
| Definitely | 1 | 0 | 0 | 0 |
| | | | | |
| **Serious Adverse Events[c]** | | | | |
| Participants with at least 1 event | 24 (17·0%) | 18 (17·0%) | 4 (10·6%) | 9 (12·8%) |
| Total events reported | 35 | 24 | 9 | 10 |
| Total number of deaths | 1 | 0 | 0 | 0 |
| | | | | |

[a] COVID Group X, were those who were unassigned to a COVID group as they were lost to follow-up at the time the COVID groups were assigned, or they had withdrawn from the study.

[b] Adverse events were defined as any untoward medical occurrence, regardless of causal relationship with treatment, and not meeting the criteria for a serious adverse event.

[c] Serious adverse events were defined as any untoward occurrence that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect, or was otherwise considered medically significant by the investigator. No serious adverse events were deemed to be related to receiving physiotherapy.

# Figure 2. Continuous outcome measures

**Continuous outcome measures, effect size (ES) and 95% confidence interval (CI) at six and 12-months, adjusting for baseline values and sites and standardising by baseline values of each outcome due to differences in scale.**

Footnotes: Abbreviations: SP=specialist physiotherapy; TAU=treatment as usual; N=maximum number of participants; n=number of participants with available data.

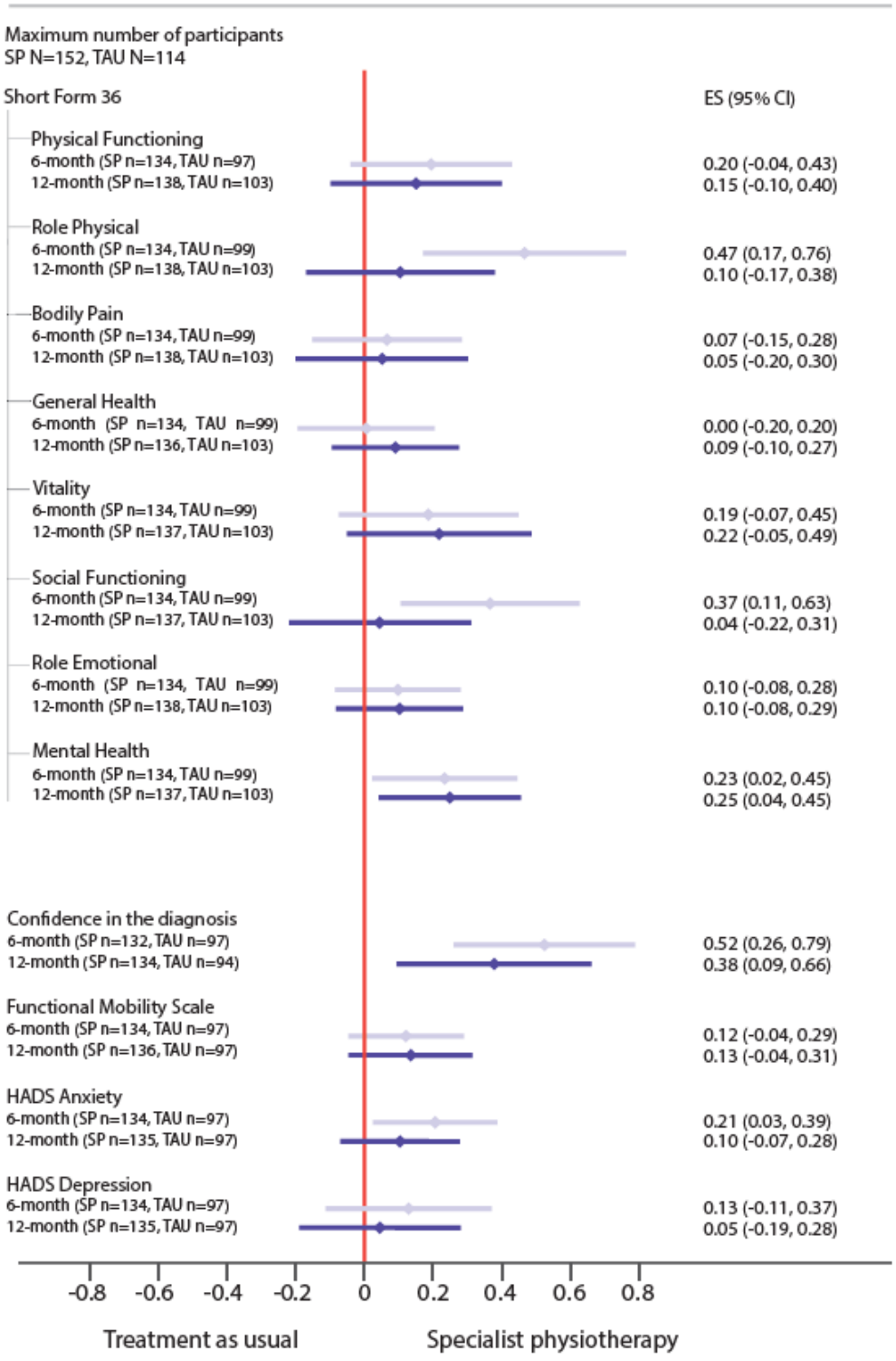
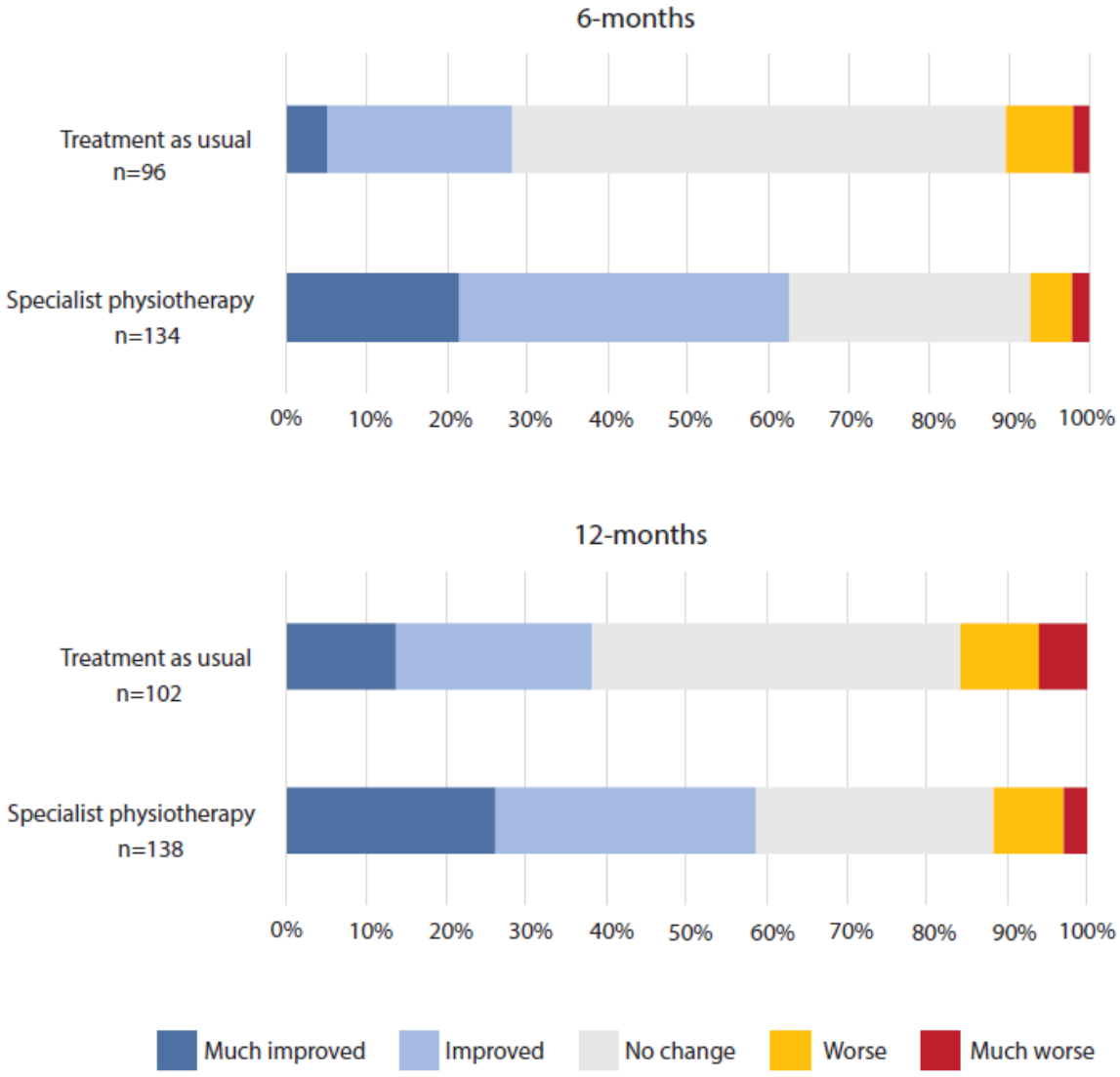


**Figure 3. Participant rated Clinical Global Impression scale of Improvement at six- and 12-months.**

Legend: Participant rated perception of improvement, in answer to the question, "After physiotherapy, the problem with my movement is…" Odds ratio of improvement at 6-months for specialist physiotherapy compared treatment as usual was 4·7 (95% CI 2·6 to 8·6); odds ratio at 12-months 2·3 (1·4 to 3·9).



# PANEL: RESEARCH IN CONTEXT

**Evidence before this study**

We searched Ovid Medline from inception (1946 to May 09, 2023) with the following search strategy: conditions terms ("functional neurological", "functional movement", "psychogenic", "conversion", "hysterical", "hysteria", "non-organic", "nonorganic", "functional neurological symptom disorder", "dissociative neurological symptom disorder", and "Conversion Disorder/"); AND intervention terms ("physiotherapy", "physical therapy", "rehabilitation", "exercise", "Physical Therapy Modalities/" and "Neurological Rehabilitation/"); AND study terms ("Randomized Controlled Trial/", "Cohort Studies/", and "Case Reports"). We conducted additional searches using Google Scholar and we hand searched reference lists.

There were no powered randomised controlled trials (RCT). There were two randomised studies, each with 60 participants. The first compared 3-weeks of inpatient multidisciplinary rehabilitation for functional gait disorder to a four-week waitlist control, after which the control group crossed over to receive the intervention. The other randomised study was the feasibility study for the current RCT, where we tested similar intervention and control conditions. In both studies, scores of physical health but not mental health were maintained at 12-months (uncontrolled follow-up data) and six-months respectively. Our search identified 15 single patient case studies, 36 cohort studies (with subject numbers ranging from 3 to 305), and one RCT comparing hypnosis and multidisciplinary rehabilitation to multidisciplinary rehabilitation alone (the two arms of this trial are considered as a single cohort for the purposes of this review).

In summary, there are a growing number of studies describing promising outcomes from physical-based interventions for FMD. There has been an absence of evidence from adequately powered RCTs, and a lack of controlled follow-up data beyond 6-months.

**Added value off this study**

The Physio4FMD trial is the first fully-powered RCT of a physical-based intervention for FMD and the largest randomised study of people with FMD published to date. The intervention was protocolised and was described in a way that allows it to be replicated and refined by others. We have also shown that large, randomised trials of a complex intervention involving people with FMD can be delivered with high levels of compliance and retention.

**Implications of all the available evidence**

We found no difference between specialist physiotherapy and treatment as usual for our primary outcome, SF36 Physical Functioning. Both specialist and non-specialist physiotherapy groups improved in measures of physical function. In secondary outcomes, more participants in the specialist physiotherapy group rated their motor symptoms improved. Specialist physiotherapy also had a superior effect on measures of mental health and self-efficacy. The results also suggest that physiotherapy, where patients are selected for treatment and physiotherapists are supported by experienced clinicians, is safe. However, there were high rates of unrelated serious adverse events, reflecting the complex nature of this patient population, the existence of multi-comorbidity and the need for multidisciplinary support. Taken together with all the available evidence, physiotherapy appears to be a valuable treatment for selected people with FMD.

## Contributors

GN led the study and wrote the first draft of the manuscript. GN, AC, ME, LG, RH, JM, LM, IN, MR, JS contributed to the study design and funding acquisition and were involved at all stages. GN and KH designed the trial intervention, wrote the intervention workbook and treatment manual, trained the physiotherapists, and provided supervision to the specialist physiotherapist group. LM and TL designed and completed the statistical analysis. BSS and HN were trial managers. AMS was the lead research assistant and verified the data. GN and BSS also verified the data. All authors were members of the Trial Management Group. All authors helped to interpret the data, to critically revise the manuscript for important intellectual content and approved the final version. All authors had full access to all the data in the study and accept responsibility to submit for publication.

## Declaration of interests

GN receives research funding from the NIHR. LM research funding from 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. 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. All other authors declare no competing interests.

## Data sharing

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. Due to our data sharing agreement and for patient confidentiality reasons, we are not able to provide access to hospital episode statistics data from NHS England and NHS Scotland.

## Acknowledgments

Thank you to our trial participants, and our service user collaborators for their important contribution to the design and management of the study. We thank our independent Trial Steering Committee and Data Monitoring and Ethics Committee for their guidance and support. We thank the PRIMENT Clinical Trials Unit team for their support, guidance and oversight of the trial set up and day to day management. This study is funded by the National Institute for Health and Care Research (NIHR), Health Technology Assessment Programme (project reference 16/31/63) – A randomised controlled trial of specialist physiotherapy for functional motor disorder (Physio4FMD). Funding has been further granted by the NIHR HTA for a 22-month costed extension. This study also represents independent research (LHG) part-funded by the NIHR Maudsley Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and King's College London. The study benefited from the support of the CRN South London Study Support Service. Thank you to FND charities FND Hope International, FND Hope UK, FND Action and FND Dimensions for their support. The views expressed are those of the authors and not necessarily those of the NIHR, NHS or the Department of Health and Social Care. For the purposes of open access, the authors have applied a Creative Commons Attribution (CC BY) licence to any Accepted Author Manuscript version arising from this submission.

# REFERENCES


1 Carson A, Lehn A. Epidemiology. In: Hallett M, Stone J, Carson A, eds. Functional Neurologic Disorders, Vol 139 of the Handbook of Clinical Neurology series. Amsterdam: Elsevier, 2016: 47–60.

2 Stone J, Carson A, Duncan R, *et al.* Symptoms ' unexplained by organic disease ' in 1144 new neurology out-patients : how often does the diagnosis change at follow-up ? 2009; **132**: 2878–88.

3 Espay AJ, Aybek S, Carson A, *et al.* Current concepts in diagnosis and treatment of functional neurological disorders. *JAMA Neurol* 2018; **75**: 1132–41.

4 Gelauff J, Stone J, Edwards MJ, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. *J Neurol Neurosurg Psychiatry* 2014; **85**: 220–6.

5 Nielsen G, Stone J, Edwards MJ. Physiotherapy for functional (psychogenic) motor symptoms: A systematic review. *J Psychosom Res* 2013; **75**: 93–102.

6 Perez DL, Edwards MJ, Nielsen G, Kozlowska K, Hallett M, Curt Lafrance W. Decade of progress in motor functional neurological disorder: Continuing the momentum. *J Neurol Neurosurg Psychiatry* 2021; **92**: 668–77.

7 Edwards MJ, Adams RA, Brown H, Parees I, Friston KJ. A Bayesian account of 'hysteria'. *Brain* 2012; **135**: 3495–512.

8 Jungilligens J, Paredes-Echeverri S, Popkirov S, Barrett LF, Perez DL. A new science of emotion: implications for functional neurological disorder. *Brain* 2022; **145**: 2648–63.

9 Nielsen G, Stone J, Matthews A, *et al.* Physiotherapy for functional motor disorders: a consensus recommendation. *J Neurol Neurosurg Psychiatry* 2015; **86**: 1113–9.

10 Nielsen G, Ricciardi L, Demartini B, Hunter R, Joyce E, Edwards MJ. Outcomes of a 5-day physiotherapy programme for functional (psychogenic) motor disorders. *J Neurol* 2015; **262**: 674–81.

11 Nielsen G, Buszewicz M, Stevenson F, *et al.* Randomised feasibility study of physiotherapy for patients with functional motor symptoms. *J Neurol Neurosurg Psychiatry* 2017; **88**: 484–90.

12 Nielsen G, Stone J, Buszewicz M, *et al.* Physio4FMD: protocol for a multicentre randomised controlled trial of specialist physiotherapy for functional motor disorder. *BMC Neurol* 2019; **19**: 242.

13 Gupta A, Lang AE. Psychogenic movement disorders. *Curr Opin Neurol* 2009; **22**: 430–6.

14 SealedEnvelope. Randomisation and online databases for clinical trials. https://www.sealedenvelope.com/ (accessed June 26, 2019).

15 Nielsen G, Holt K. Physio4FMD Programme Workbook 2.0. *St George's, University of London Online resource* 2023. DOI:https://doi.org/10.24376/rd.sgul.23967024.v1.

16 Nielsen G, Holt K. Physio4FMD Intervention Manual. *St George's, University of London Online resource* 2023. DOI:https://doi.org/10.24376/rd.sgul.23967156.v1.

17 Syddall HE, Martin HJ, Harwood RH, Cooper C, Aihie Sayer A. The SF-36: a simple, effective measure of mobility-disability for epidemiological studies. *J Nutr Health Aging* 2009; **13**: 57–62.

18 Sharpe M, Walker J, Williams C, *et al.* Guided self-help for functional (psychogenic) symptoms: a randomized controlled efficacy trial. *Neurology* 2011; **77**: 564–72.

19 Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *BMJ* 1993; **306**: 1437–40.

20 Graham HK, Harvey A, Rodda J, Nattrass GR, Pirpiris M. The Functional Mobility Scale (FMS). *J Pediatr Orthop* 2004; **24**: 514–20.

21 Moss-Morris R, Weinman J, Petrie KJ, Horne R, Cameron LD, Buick D. The Revised Illness Perception Questionnaire (IPQ-R). *Psychol Health* 2002; **16**: 1–16.

22 Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; **67**: 361–70.

23 Yang Y, Rowen D, Brazier J, Tsuchiya A, Young T, Longworth L. An exploratory study to test the impact on three 'bolt-on' items to the EQ-5D. *Value Health* 2015; **18**: 52–60.

24 Goldstein LH, Mellers JDC, Landau S, *et al.* COgnitive behavioural therapy vs standardised medical care for adults with Dissociative non-Epileptic Seizures (CODES): a multicentre randomised controlled trial protocol. *BMC Neurol* 2015; **15**: 98.

25 NHS Digital. Hospital Episode Statistics. DOI:https://digital.nhs.uk/data.

26 ISD Services | Electronic Data Research and Innovation Service (eDRIS) | ISD Scotland. https://www.isdscotland.org/products-and-services/edris/ (accessed Oct 2, 2023).

27 Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16**: 606–13.

28 Carson AJ, Stone J, Hansen CH, *et al.* Somatic symptom count scores do not identify patients with symptoms unexplained by disease: a prospective cohort study of neurology outpatients. *J Neurol Neurosurg Psychiatry* 2015; **86**: 295–301.

29 ICH Expert Working Group. Guideline for Good Clinical Practice E6 (ICH-GCP). *ICH Harmonised Tripartite Guideline* 1996; **1996**: i–53.

30 MHRA. Guidance on minimising disruptions to the conduct and integrity of clinical trials of medicines during COVID-19. 2020. https://www.gov.uk/guidance/guidance-on-minimising-disruptions-to-the-conduct-and-integrity-of-clinical-trials-of-medicines-during-covid-19 (accessed Jan 5, 2022).

31 EMA. Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials. 2020. https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical_en-0.pdf (accessed Jan 5, 2022).

32 FDA. Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency Guidance for Industry, Investigators, and Institutional Review Boards For questions on clinical trial conduct during the COVID-19 pandemic, please email Clinicaltri. 2020. https://www.fda.gov/regulatory- (accessed Jan 5, 2022).

33 Marston L, Le M, Ricciardi F, *et al.* COVID-19 and the Physio4FMD trial : Impact , mitigating strategies and analysis plans. *Contemp Clin Trials Commun* 2023; **33**: 101124.

34 Keurentjes JC, Van Tol FR, Fiocco M, Schoones JW, Nelissen RG. Minimal clinically important differences in health-related quality of life after total hip or knee replacement: A systematic review. *Bone Joint Res* 2012; **1**: 71–7.

35 Nicholson TR, Carson A, Edwards MJ, *et al.* Outcome measures for functional neurological disorder: A review of the theoretical complexities. *Journal of Neuropsychiatry and Clinical Neurosciences* 2020; **32**. DOI:10.1176/appi.neuropsych.19060128.

36 Pick S, Anderson DG, Asadi-Pooya AA, *et al.* Outcome measurement in functional neurological disorder: a systematic review and recommendations. *J Neurol Neurosurg Psychiatry* 2020; : jnnp-2019-322180.

37 Nielsen G, Ricciardi L, Meppelink A, Holt K, Teodoro T, Edwards MJ. A simplified version of the Psychogenic Movement Disorders Rating Scale: The Simplified Functional Movement Disorders Rating Scale (S-FMDRS). *Mov Disord Clin Pract* 2017; **4**: 710–6.

38 Jordbru AA, Smedstad LM, Klungsøyr O, Martinsen EW. Psychogenic gait disorder: A randomized controlled trial of physical rehabilitation with one-year follow-up. *J Rehabil Med* 2014; **46**: 181–7.

# Physio4FMD Study Group

| FIRST NAME | SECOND NAME |
|---|---|
| Emily | Beaves |
| David | Breen |
| Christine | Burness |
| Simone | Caddy |
| Hannah | Callaghan |
| Andrew | Carberry |
| Luke | Chetham |
| Andrea | Clyne |
| Susie | Cobb |
| Jan | Coebergh |
| Lewis | Cook |
| Patrick | Cookson |
| Paul | Cooper |
| Clare | Diamond |
| Lee | Drake |
| Victoria | Dunn |
| Paula | Gardiner |
| Thomas | Gilbertson |
| Dawn | Golder |
| Rebecca | Gregory |
| Helen | Harbinson |
| Rory | Higgins |
| Ingrid | Hoeritzauer |
| Laura | Irvine |
| Jeremy | Isaacs |
| Emily | Jay |
| Danielle | Kearney |
| Uzma | Khan |
| James | Magro |
| Elizabeth | Mallam |
| Eleanor | Harle |
| Luke | Massey |
| Sarah | McRae |
| Shagun | Misra |
| Steph | Mitchell |
| Cameron | Moss |
| Esther | Mountain |
| Shona | Murray |
| Rachel | Newby |
| Marianne | Novak |
| Annie | Ross |
| Anna | Rutherford |

| | |
|---|---|
| Gillian | Sare |
| Rhiannon | Sears |
| Will | Sedley |
| Sumeet | Singhal |
| Biba | Stanton |
| Charlotte | Stone |
| Gillian | Szeto |
| Lauren | Tarr |
| Tiago | Teodoro |
| Volker | Teweleit |
| Michael | Walsh |
| Rhian | Warman |
| Mahinda | Yogarajah |

1