Physio4FMD PROTOCOL

Long title of the trial	A randomised controlled trial of Specialist Physiotherapy for Functional Motor Disorder
Short title of trial	Physio4FMD
Version and date of protocol	Version 6.0, 09/02/2021
Sponsor	St George's, University of London
Sponsor protocol number	17.0258
Funder (s)	NIHR Health Technology Assessment (HTA)
Trial registration number	ISRCTN56136713
Phase of trial	III
Sites	Multiple
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Sponsor Representative:	Mr Joseph Montebello Research Governance and Facilitation Officer Joint Research and Enterprise Office St George's, University of London jmontebe@sgul.ac.uk

SIGNATURES

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles of GCP, Priment CTU's SOPs (unless otherwise stated in the protocol), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator: Glenn Nielsen

Sign:

Date:

Sponsor Representative: Joseph Montebello

Sign:

Date:

Priment CTU Representative: Anne Marie Downey

Sign:

Date:

This Protocol template is intended for use with UK sites only.

VERSION HISTORY

Version number	Version date	Reason for Change
1.0	17/02/2018	Final first version.
2.0	02/07/2018	Addition of Trial Manager contact details Minor changes to exclusion criteria no. 3 Error corrected on summary page exclusion criteria Summary page adjusted to reflect inclusion from inpatients as well as outpatients Addition of Extended PHQ outcome measure Addition of Confidence in correctness of diagnosis of FMD outcome measure Changes to the wording of the SAE reporting section
3.0	15/03/2019	Amending reference to all participants requiring at least 24 hours to consider the PIS before consent. Changing the screening period from 28 days to 8 weeks. Amending the start and end months of the internal pilot phase
4.0	11/02/2020	Updating the sponsor representative Addition of Prof Irwin Nazareth as a collaborator Other minor changes to collaborator job titles and contact details Updating the sample size calculation to reflect up to 30% drop out Adding text message and email contact to allow follow up of missing follow up outcome measures Correcting the error WPAI-GH to WPAI-SHP in section 16 Some minor grammatical corrections
5.0	28/10/2020	Addition of COVID-19 risk assessment and management strategy statement
6.0	09/02/2021	Addition of a qualitative interview with trial physiotherapists

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DSM-5	Diagnostic Statistical Manual of Mental Disorders
DMEC	Data Monitoring and Ethics Committee
eICF	Electronic Informed Consent Form
Non-CTIMP	Clinical Trial without an Investigational Medicinal Product
FMD	Functional Motor Disorder
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
HRA	Health Research Authority
HTA	Health Technology Assessment (NIHR funding stream)
ICF	Informed Consent Form
ICD-10	International Classification of Disease, version 10
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
JREO	Joint Research and Enterprise Office, SGUL
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health Research
PI	Principal Investigator
PIS	Participant Information Sheet
PHQ-15	Patient Health Questionnaire-15
PPI	Patient and Public Involvement (in research)
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Document Verification
SF36	Short Form 36 (Quality of life questionnaire)

SF36-PF	Short Form 36 Physical Function Domain
SGUL	St George's, University of London
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAU	Treatment as usual
TMG	Trial Management Group
TSC	Trial Steering Committee

3 TRIAL PERSONNEL

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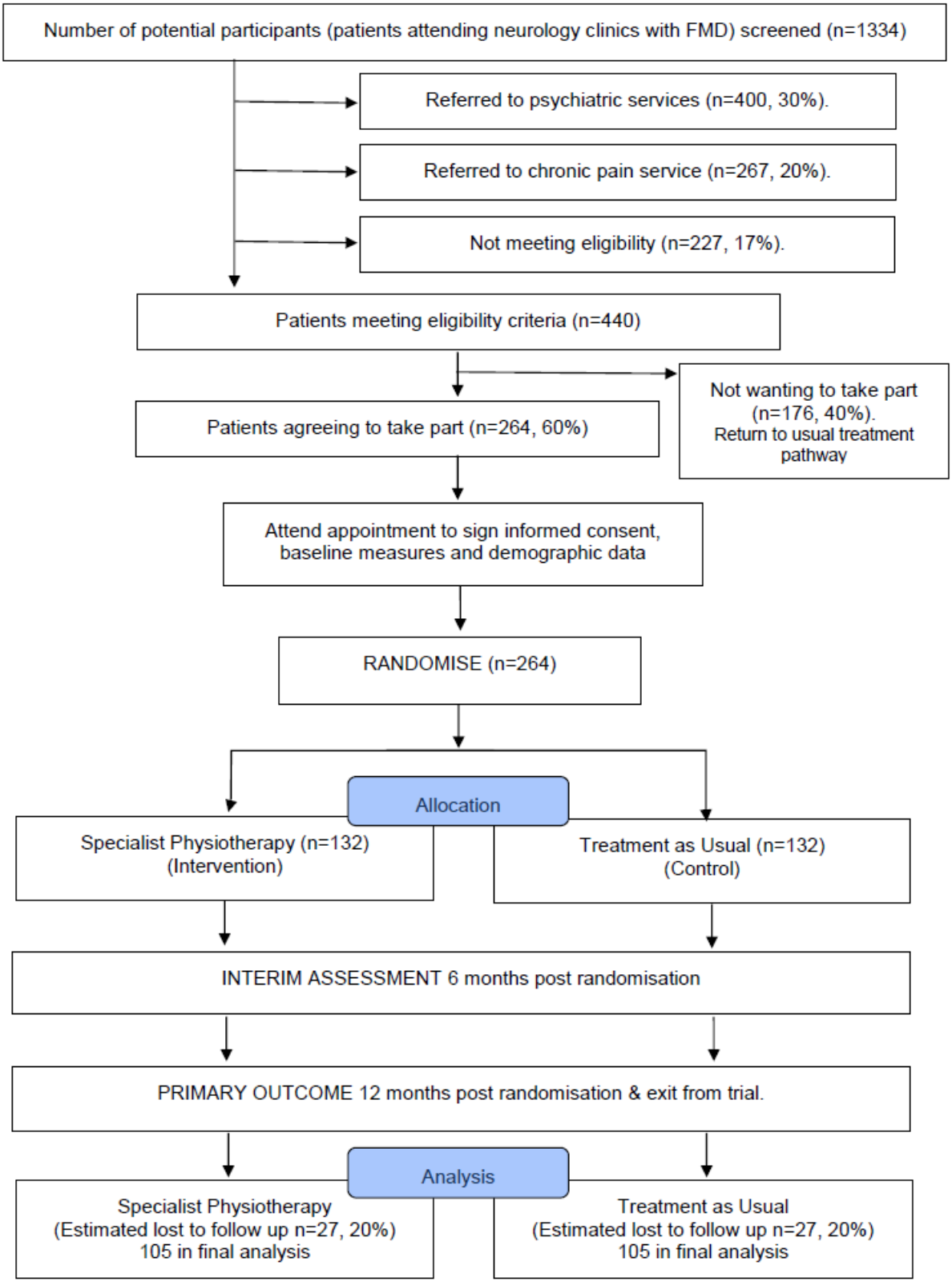
4 SUMMARY

Title:	A randomised controlled trial of Specialist Physiotherapy for Functional Motor Disorder
Short title:	Physio4FMD
Phase of trial:	III
Objectives:	Primary objective: To evaluate the effectiveness of specialist physiotherapy compared to treatment as usual in reducing disability at 12 months. Secondary objectives: • To undertake an economic evaluation to assess the cost-effectiveness of the intervention compared to treatment as usual. • To evaluate the effect of physiotherapy compared to treatment as usual on participants' perception of change to their movement problem, health related quality of life, anxiety and depression, illness beliefs and understanding, employment, health service use, and satisfaction with treatment.
Type of trial:	Pragmatic, multi-centre, single-blind, parallel group, randomised controlled trial in adults with functional motor disorder (FMD).
Trial design and methods:	Patients with FMD will be recruited from outpatient neurology clinics and inpatients due to be discharged. Participants will be randomised to receive the study intervention – a novel specialist physiotherapy treatment protocol, or treatment as usual (TAU), which consists of a referral to community physiotherapy suitable for patients with neurological symptoms. The primary assessment is at 12 months, with a 6 months interim assessment. The primary outcome measure is the Physical Function domain of the Short Form 36 questionnaire.
Trial duration per participant:	12 months
Estimated total trial duration:	43 months
Planned trial sites:	8 Sites, including St George's Hospital London, Western General Hospital Edinburgh, Royal Hallamshire Hospital Sheffield, North Bristol NHS Trust, Addenbrooke's Hospital Cambridge, Queen Elizabeth Hospital Glasgow, NHS Tayside Dundee, Walton Centre NHS Trust Liverpool, Dorset County Hospital, Salford Royal NHS Trust, Newcastle Upon Tyne Hospitals Trust, King's College Hospital NHS Trust.
Total number of participants planned:	Minimum of 264 (132 per group); maximum of 300 (150 per group)

Main inclusion/exclusion criteria:	Inclusion criteria: 1. New or returning patients presenting to participating outpatient neurology clinics and neurology inpatients. 2. The patient has a "clinically definite" diagnosis of FMD according to the Gupta and Lang diagnostic classification criteria [1]. 3. Age 18 or over. 4. Diagnostic investigations have come to an end. 5. The patient is accepting of the intervention. 6. Motor symptoms must be sufficient to cause significant distress or impairment in social, occupational or other important areas of functioning (subjectively described by the patient), independent of other comorbidities. Exclusion criteria: 1. The recruiting neurologist deems the patient to have severe psychiatric comorbidity, including factitious disorder, self-harm, anxiety and depression, which would interfere with the patient's ability to participate in physiotherapy. 2. The patient has an organic diagnosis that explains the majority of their symptoms or disability. 3. The patient has pain, fatigue or dissociative seizures that would interfere with their ability to engage in the trial physiotherapy intervention. 4. Disability to the extent that the patient requires assistance for toileting. 5. The patient is unable to attend 9 sessions of physiotherapy over a 3 week period, within 6 weeks of initial neurology consultation. 6. Ongoing unresolved compensation claim or litigation. 7. The patient has no fixed address or is seeking rehousing through their council for disability access reasons. 8. Unable to understand English sufficiently to complete questionnaires. 9. The patient has a documented learning disability that prevents them from answering questionnaires independently. 10. The patient lacks capacity to give informed consent.
Statistical methodology and analysis:	Using intention to treat principles, the intervention and control groups will be compared at 12 months using random effects linear modelling or random effect logistic modelling as appropriate for primary and secondary outcomes. Modelling will account for baseline measures of the outcomes. We will conduct an exploratory analysis using random effects logistic regression to investigate whether baseline measures are predictive of a good outcome.

5 TRIAL FLOW CHART

Flow Chart of Trial with estimated recruitment and drop out figures



6 INTRODUCTION

6.1 BACKGROUND

Functional motor disorder (FMD) is a specific presentation of neurological symptoms affecting movement that are not caused by a known disease process. It is classified in the Diagnostic Statistical Manual of Mental Disorders (DSM-5) [2] under the broader category of "Conversion disorder (functional neurological symptom disorder)" and in the International Classification of Disease (ICD-10) [3] as "Dissociative motor disorder". The diagnosis is distinct from malingering and factitious disorder. Patients with FMD typically present with one or a combination of weakness, tremor, dystonic postures or an altered gait pattern. These symptoms cause distress and disability equivalent to or greater than those caused by neurological disease [4]. The diagnosis is generally made by a neurologist and where possible it is based on positive diagnostic clinical tests. In addition, other potential causes of neurological symptoms (organic disease) are excluded with appropriate targeted investigations (usually an MRI and neurophysiology or laboratory tests) [5]. Functional neurological disorder is among the most common diagnoses made in outpatient neurological clinics and was second only to headache in a study of 3781 consecutive new NHS neurology referrals in Scotland over a 14 month period [6]. Furthermore the diagnosis is stable; a systematic review found that misdiagnosis or emergence of an organic cause for symptoms was rare [7].

The long term outcome of FMD is generally considered poor. A systematic review of prognosis found that approximately 40% of patients were the same or worse at long term follow up of 7 years and the majority of patients remain symptomatic [8]. Corresponding to the high incidence and disability caused by FMD is a substantial economic burden. Costs are associated with extensive health and social care utilisation, as well as high rates of unemployment and receipt of disability benefits [4]. There are no studies specifically assessing the costs of FMD, but the cost of medically unexplained symptoms as a whole (which includes non-neurological symptoms such as gastro-intestinal symptoms and pain) in England alone was estimated to be £18 billion annually, based on data collected for the period 2008-2009 [9]. This figure took into account healthcare use, quality of life effects and output losses. The cost of additional healthcare was estimated to be £3 billion per year, representing 10% of total NHS expenditure on healthcare services for the working age population.

Historically FMD has been understood from a predominantly psychological point of view, with its onset linked to childhood abuse or neglect and adverse events in later life. However, it is increasingly recognised that such explanations do not apply to a sizeable proportion of patients with FMD and broader biopsychosocial aetiological models are more relevant. This change in perspective is reflected in the most recent version of the DSM-5, where the requirement for the presence of a psychological stressor preceding symptom onset has been downgraded from essential to a supportive criterion. In line with a broader

biopsychosocial explanatory framework is the recent progress made in understanding how symptoms are produced and experienced as involuntary. Neurobiological mechanisms related to the focus of motor attention and illness beliefs/expectations of abnormal movement have been proposed as mechanisms driving symptoms and these provide a rationale for a physically-orientated treatment approach [10].

The role of attention in FMD can be easily demonstrated as functional motor symptoms require attention to manifest. When the patient's attention is distracted away from their symptoms, there is a reduction or disappearance of the movement disorder [10]. Conversely, there is a worsening of symptoms when the patient's attention is drawn towards their body. This can be addressed with physiotherapy treatment by helping the patient to understand the role of attention and retraining movement with diverted attention.

Expectation as a symptom mechanism relates to the patient's expectation or belief that their movement will be abnormal and this is thought to influence motor output at a preconscious level. Expectation as a symptom mechanism has been described in terms of the theory of active inference of brain function [11]. In brief, active inference refers to how the brain operates using predictive "pre-programmed" models to control movement. The models are based on our learnt experiences of interacting with the world. An expectation that movement will be abnormal (e.g. muscle weakness/paralysis) alters the predictive "pre-programmed" model of movement. This concept can be likened to the experience of picking up an object that you expected to be heavy but turns out to be light. The expectation is inaccurate resulting in inappropriate motor output - overshooting the movement. Physiotherapy can address illness beliefs and expectations of abnormal movement through education and by demonstrating to the patient that their movement can be normal using techniques that distract their attention away from their symptoms.

6.2 CLINICAL DATA

The evidence base for physiotherapy for FMD is limited but growing. The first controlled trial of physical rehabilitation was published in 2014, in the form of a delayed start design (described in the paper as a crossover design) [12]. In this study 60 patients with a functional gait disorder were randomised to a 3 week inpatient physical rehabilitation programme or a 4 week waiting list control. Group comparisons demonstrated a statistically significant improvement with treatment across a range of physical and quality of life outcome measures. The mean differences immediately after the intervention were 6.9 units in the Functional Mobility Scale (15 point range), 8.4 Functional Independence Scale units (108 point range), and 12 SF12 physical domain units (maximum score 100). Improvements in outcome measure scores were sustained at 12 months follow up, except for the SF12 mental health domain which showed an immediate treatment effect but was no longer statistically different at 12 months.

Our group has recently completed a single centre, randomised feasibility study of physiotherapy for FMD [13]. In this study 60 patients were randomised to either our specific physiotherapy protocol for FMD or a treatment as usual control (consisting of referral to standard community physiotherapy). Participants were followed up at 6 months. We found a high rate of recruitment and retention. Thirty-two per cent of patients with FMD seen in the recruiting neurology clinics were suitable for the physiotherapy intervention and therefore met the inclusion criteria. 90% of this group consented to participate in the trial and only 5% were lost to follow up (60 participants were recruited in 9 months). Participants rated the intervention as highly acceptable. We tested a range of physical, mental health and quality of life outcome measures. At 6 month follow up, the intervention group scored higher on measures of physical function but there were no differences in scores of mental health. The Short Form 36 Physical Function domain (SF36-PF) showed a large mean difference between groups, adjusted for baseline scores this value was 19.8 (95% CI 10.2, 29.5, Cohen's d=0.7). In a patient rated 5-point Likert scale of impression of change, 72% of the intervention group rated their symptoms as improved at 6 months, compared to 18% in the control group. Based on the EQ-5D-5L assessment, the additional quality adjusted life years (QALYs) with the intervention were 0.08 (95% CI 0.03, 0.13). Once cost savings for other health and social care services for the specialist physiotherapy group of £474 per patient were factored into the analysis, the mean incremental cost per QALY gained was £9076, which is below the threshold for cost effectiveness of £20,000 per QALY gained.

The physiotherapy intervention being investigated in this trial has been modified based on feedback from over 100 patients who have undergone the treatment. For example, a follow up appointment at 3 months post treatment has been added to the treatment protocol. The intervention has also been modified from the feasibility study to allow the treatment protocol to be delivered over a 3 week period, rather than intensively over 5 days. This change has been made to give some flexibility in order to accommodate participants' lifestyles and the normal service structures of NHS outpatient physiotherapy departments.

6.3 RATIONALE AND RISKS/BENEFITS

There are substantial numbers of patients with FMD unable to access specialist treatment. Our feasibility study (and previous work) [13–15] demonstrated that with the study intervention, these patients made significant improvements in disability and quality of life outcomes, despite long symptom durations and previous unsuccessful attempts with non-specialist treatments, including physiotherapy. If proven effective in a large trial, the study intervention could be swiftly rolled out across the NHS, where physiotherapists are already seeing these patients and are interested in doing so, but lack the specific evidence base to guide successful treatment [16]. The potential for NHS cost savings as well as social welfare savings is substantial, given the prevalence of this problem and associated high rates of unemployment, receipt of disability benefits, and health and social care utilisation [4].

6.4 ASSESSMENT AND MANAGEMENT OF RISK

The physiotherapy intervention carries little risk to the participants. Previous studies of physiotherapy and physical rehabilitation for FMD have not reported serious adverse events associated with the intervention [12,13,17]. The study intervention fits within the scope of usual physiotherapy practice and resembles standard NHS physiotherapy programmes for chronic pain provided around the UK.

There is a minor risk that participating in physiotherapy may exacerbate psychological distress, however this was not a significant problem in the preceding cohort and feasibility studies. While patients with FMD often have higher rates of self-reported anxiety and depression than healthy controls, it is now recognised that psychiatric comorbidity and a past history of psychological trauma are not as common as once thought [18]. We will mitigate the potential for the intervention to cause an exacerbation of psychological distress by excluding patients with a higher risk of developing mental health related problems. The exclusion criterion is as follows: “The recruiting neurologist deems the patient to have severe psychiatric comorbidity, including factitious disorder, self-harm, anxiety and depression, which would interfere with the patient’s ability to participate in physiotherapy.” This exclusion criterion is judged based on a comprehensive assessment by the neurologist. We have opted not to use a screening tool or questionnaire to exclude patients at higher risk of metal health related problems because no one tool is suitable for this purpose. The recruiting consultant neurologists who will screen patients have been selected for their clinical experience and expertise in treating patients with FMD and psychiatric comorbidity.

In this study protocol and previous developmental work we have carefully considered the psychological needs of the participants and psychological risk factors in order to minimise the potential for mental health related adverse events. The trial co-applicants have extensive clinical and research experience in FMD, this includes the fields of psychiatry (Dr Alan Carson), neurology (Prof Mark Edwards, Dr Jon Stone, Prof Markus Reuber), psychology (Prof Laura Goldstein), general practice with specialist mental health experience (Dr Marta Buszewicz), and physiotherapy (Dr Glenn Nielsen and Prof Jonathan Marsden). In the event of a mental health related serious adverse event (SAE), there will be a SOP to follow. This will include following the local trust procedure (which, depending on the situation may include delivering the participant to A&E, contacting the local mental health crisis team, and informing the GP) and informing the chief investigator.

There are minor safety risks of falls associated with rehabilitation of patients with gait and balance problems. In general, patients with FMD affecting gait and balance are considered to have a low risk of injury due to falls. Patients with functional gait and balance disorders often exhibit a “walking-on-ice” pattern (also called astasia-abasia), where they subjectively feel unbalanced but objectively display good balance reactions by shifting their centre of gravity to the outer regions of their base of support [5]. Physiotherapists are expert at assessing and minimising falls risks and this forms part of normal physiotherapy practice

(e.g. advice regarding footwear, uncluttering the home environment, use of rails, etc; as well as rehabilitation to improve gait, balance and confidence). Chronic pain and fatigue are common in patients with FMD and these may be exacerbated with rehabilitation. However this should be transient and physiotherapy interventions routinely involve addressing pain and fatigue. Pain and fatigue will be monitored with the study outcome measures.

The trial management group (including the above named professionals) will discuss SAEs and refer SAEs that are determined to be related to the intervention to the Data Monitoring and Ethics Committee (DMEC). We will request that participants inform us of any difficulties encountered during the study, including a routine adverse event screen during study assessments. We will consider the need to make changes as necessary.

We have considered the needs of the physiotherapists providing the trial intervention. Physiotherapists regularly see patients with FMD as part of their usual practice and generally have support within the clinical role. In addition to this, the physiotherapists providing the trial intervention will be provided with additional supervision by Glenn Nielsen and other experienced clinicians participating in the trial will be available for support.

As the study is a single blind study, there is a small risk that assessors may become unblinded during follow up data collection. We will minimise this risk by the following: assessors will remind participants at each stage that they must not discuss their intervention with their assessor; both groups are delivered through the same platform and receive the same measures; if an assessor does become unblinded we will make a note of this and ask an alternative assessor to complete future outcome measures for this participant.

6.4.1 COVID-19 RISK ASSESSMENT AND MANAGEMENT STRATEGY

All patients attending hospital sites for research visits will be expected to abide by the NHS Trust and University policies on COVID-19; including wearing suitable PPI (provided by NHS Trust on arrival), adhering to the visitor policy on social distancing and following the one-way routing systems whilst on site. All research personnel will comply with the NHS Trust and University policies on COVID-19.

Due to the nature of this study requiring specialist physiotherapist treatment, it is not possible to align the schedule of study assessments with typical clinical pathways. The additional risk of exposure to COVID-19 has been assessed by the Chief Investigator and research team, as well as the relevant Trust Clinical Care Group Lead and deemed acceptable. Patients will be made explicitly aware of the additional risk of a research-specific visit on site, that they are under no obligation to participate in the research without prejudice to their routine care and will be checked for symptoms by the research team prior to attending the site and again on the day of the visit. As the situation evolves, local research teams will be required to adhere to the most up to date NHS Trust and University policies regarding all on-site research activity.

The schedule of study assessment has been designed for remote follow up at 6 and 12 months which will minimise the additional risk of exposure to COVID-19 to both research participants and staff through participation in this research.

7 OBJECTIVES

The overall aim is to evaluate the clinical and cost-effectiveness of a Specialist Physiotherapy protocol for FMD.

Primary: The primary objective is to evaluate the effectiveness of Specialist Physiotherapy compared to treatment as usual (TAU) in reducing disability, measured by the Physical Function domain of the SF36-PF at 12 months post randomisation.

Secondary: The secondary objectives are to evaluate:

1. The effectiveness of Specialist Physiotherapy compared to treatment as usual at reducing **objective measures of health service use** at 12 months, based on Hospital Episode Statistics (HES) and equivalent data from NHS Scotland (ISD Scotland; NHS Digital).
2. The effectiveness of Specialist Physiotherapy compared to treatment as usual at reducing **subjective measures of health service use** at 12 months using the Client Services Receipt Inventory (CSRI) [21].
3. The effectiveness of Specialist Physiotherapy compared to treatment as usual in improving **mobility** at 6 and 12 months post randomisation, measured by the Functional Mobility Scale [22].
4. The effectiveness of Specialist Physiotherapy compared to treatment as usual at improving **health-related quality of life** at 6 and 12 months post randomisation, measured by the Short Form 36 [23].
5. **The patient's perception of change** at 6 and 12 months post randomisation using the Clinical Global Impression Scale of Improvement (CGI-I) [24,25].
6. The influence of Specialist Physiotherapy compared to treatment as usual on **understanding and illness beliefs** at 6 and 12 months post randomisation, measured by the Revised Illness Perception Questionnaire [26].
7. The influence of Specialist Physiotherapy compared to treatment as usual on self-reported **anxiety and depression** at 6 and 12 months post randomisation, measured by the Hospital Anxiety and Depression Scale [27].
8. The **cost-effectiveness** of Specialist Physiotherapy compared to treatment as usual at 12 months, in a comprehensive health economic analysis, using the CSRI to collect health service use, validated using HES data and the EQ-5D-5L to calculate Quality Adjusted Life Years [28,29].
9. The effectiveness of Specialist Physiotherapy compared to treatment as usual in **enabling continued employment or facilitating return to work** at 12 months post randomisation. This will be assessed by monitoring employment status and use of the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP) [30].

10. The **treatment fidelity** of the manualised Specialist Physiotherapy intervention and the implications for rolling out the intervention across the NHS.
11. The **patient's satisfaction** with their allocated treatment condition, as measured by a feedback survey.
12. The influence of the number of **somatic symptoms reported at baseline** assessment on treatment outcome at 6 and 12 months post randomisation, measured by the Extended Patient Health Questionnaire-15 [31,32].
13. The impact of Specialist Physiotherapy compared to treatment as usual on the participant's **confidence that their diagnosis of FMD is correct** at 6 and 12 months post randomisation, using a 10 point scale.

8 OUTCOMES

8.1 PRIMARY OUTCOMES

The primary outcome is the **Physical Function domain of the Short Form 36** questionnaire **(SF36-PF)**, measured at 12 months post randomisation.

8.2 SECONDARY OUTCOMES

1. Short Form 36 [33]
2. Functional Mobility Scale [22]
3. Revised Illness Perception Questionnaire [26]
4. Hospital Anxiety & Depression Scale [27]
5. Clinical Global Impression Scale of Improvement, 5-point scale (CGI-I)
6. EQ-5D-5L [28]
7. Client Service Receipt Inventory [21]
8. Work Productivity & Activity Impairment Questionnaire (WPAI) [34]
9. Fatigue State (single question 5-point scale based on EQ-5D-5L) [35]
10. Extended Patient Health Questionnaire-15 (extended PHQ-15) [31,32]
11. Confidence in correctness of diagnosis of FMD (10 point scale) [24]

The CGI-I is a 5-point scale, which will be collapsed into 2 groups, good outcome and poor outcome. Good outcome will be defined as ratings of "much improved" or "improved" and poor outcome will be defined as rating of "same", "worse", or "much worse".

8.3 SAMPLE SIZE AND RECRUITMENT

8.3.1 SAMPLE SIZE CALCULATION

The sample size was calculated by trial statistician Dr Louise Marston. The calculation uses data from the preceding single centre feasibility study [13]. Included below are the workings of the calculation, which were carried out using Stata. The workings are annotated with numbers, which are referred to as superscripts in the commentary.

Workings:

```
disp 11*0.8
8.8 (cluster size 9, allowing for 20% attrition)                          1.

disp 1+(9-1)*0.05                                                         2.
1.4

sampsi 0 0.41, sd(1) pre(1) post(1) r1(.55) method(ancova) ratio(1.4)     3.

Estimated sample size for two samples with repeated measures
Assumptions:
                                     alpha =   0.0500  (two-sided)
                                     power =   0.9000
                                        m1 =        0
                                        m2 =      .41
                                       sd1 =        1
                                       sd2 =        1
                                     n2/n1 =     1.40
           number of follow-up measurements =        1
            number of baseline measurements =        1
   correlation between baseline & follow-up =    0.550

Method: ANCOVA
 relative efficiency =    1.434
    adjustment to sd =    0.835
        adjusted sd1 =    0.835

 Estimated required sample sizes:
                  n1 =       75 (TAU)
                  n2 =      105 (intervention)                            4.

di 75*1.4
105                                                                       5.

di 210/0.8
262.5 (round to 264 =  132 in each group)                                 6.
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Assuming an intervention cluster size of 11 after assuming 20% drop out, with 8 therapists; after 20% drop out, this reduces the cluster size to 9[1]. The inflation factor (design effect) for a cluster size of 9 is 1.40[2]. We assume a difference of 0.41 standard deviations (SD) between intervention and TAU groups (based on an assumed standard deviation of 22; 9/22=0.41 of a SD), with one pre and one post randomisation measurement of the primary outcome and a correlation of r=0.55 between the pre and post randomisation SF36-PF measurements.

Using the ANCOVA method, with the design effect of 1.4[3] calculated in[2], 90% power and 5% significance. This unequal allocation matches the design effect not accounting for clustering to ensure that the sample size accounting for clustering in the intervention group has a 1:1 ratio. The unequal ratio gives 75 in the TAU arm and 105 in the intervention[4]. Step[5] equalises the ratio; Step[6] inflates for 20% drop out. The final sample size is 264 (132 in each arm).

The sample size was updated to reflect a more conservative estimate of retention based on retention rates at 6 months post randomisation. We will now allow for up to 30% attrition. To achieve 90% power, we need 105 participants in each group at the primary outcome assessment at 12 months. We will recruit up to the end of April 2020, or to a maximum of

300 (whichever comes first). The maximum figure of 300 allows for a 30% drop out (step[6] would change to 210*0.7). Our minimum figure will be 264, which allows for a 20% drop out and was our original recruitment target.

8.3.2 PLANNED RECRUITMENT RATE

Patients with FMD are common in outpatient neurology clinics, making up 3% of all new referrals; this number is higher in specialist neurology clinics such as the planned study sites [5,6]. We require an average recruitment rate of 13.2 participants per month to complete recruitment in 20 months. With 8 recruiting sites, we will require a recruitment rate of 1.65 participants/month/site.

9 TRIAL DESIGN

9.1 OVERALL DESIGN

The study design is a pragmatic, multi-site, single-blind, parallel group, randomised controlled trial in adults with FMD. The trial will compare a specialist physiotherapy protocol with treatment as usual (referral to community physiotherapy). Participants will be assessed at 6 and 12 months. Embedded in the trial design is an internal pilot, see below for details.

The researchers collecting outcome data, the health economists and statisticians will be blind to treatment allocation. The Trial Manager, participants and treating clinicians will not be blinded due to practical reasons.

9.2 RECRUITMENT

Participant recruitment at a site will only commence when the trial has received all ethical and local site approvals, been initiated by the Sponsor or its delegated representative and an open to recruitment letter has been issued.

Participants will be recruited from neurology inpatients and patients referred to neurology clinics at participating sites. Patients who are who are diagnosed with a “clinically definite” diagnosis of FMD [1,36] by the participating neurologist will be screened for eligibility. Potential participants are screened against the eligibility criteria, no additional screening assessments are conducted.

As per usual practice, the neurologist will explain the diagnosis to the patient following a standardised explanation that is considered best practice [37]. Patients meeting the eligibility criteria will be informed about the study by the neurologist, be given opportunity to ask questions and provided with a patient information sheet. The neurologist will then seek consent from the patient to be contacted by a member of the research team.

9.3 INTERNAL PILOT

As required by the funder, an internal pilot phase is built into the study design. The internal pilot phase will be conducted during the first half of the recruitment period to ensure

feasibility of completion of the trial within 43 months. The decision to proceed with the trial will be reviewed by the TSC after 9 months of recruitment (at the end of study month 15) who will feedback to the funder who will make the final decision. The criteria for judging the success of the pilot phase and proceeding to full trial will be based on the following:

Stop/Go Criteria for Internal Pilot	Proceed to main trial	Review feasibility of continuing with the TSC	Trial to stop
(i) RECRUITMENT RATE A recruitment rate of 13.5 participants/month is required to achieve full recruitment in 20 months (n=122 after 9 months of recruitment).	Recruitment rate of 75% or greater of the required rate. (n>92)	Recruitment rate of 50-75% of required rate. (n=61-92)	Recruitment rate is less than 50% (n<61) (but all started treatment to be completed).
(ii) SITE SETUP The internal pilot will run at a minimum of 4 sites.	If 6 sites or more set up, progress to full trial.	If 4-5 sites have been set up, we will review the feasibility of continuing with the TSC.	If fewer than 4 sites set up, we will plan for the trial to stop (but all started treatment to be completed).
(iii) PROGRAMME ATTENDANCE Participants randomised to the intervention group will attend a minimum of 50% of the programmed sessions.	If attendance is 60% or greater, progress to full trial.	If attendance is 50-60%, discuss with TSC measures to be implemented to boost attendance rate.	If attendance is less than 50%, trial to stop (but all started treatment to be completed).

The above criteria will be closely monitored and reviewed after 9 months of recruitment. If the trial is not on track, additional measures will be taken. This will include additional site visits to support set up and recruitment processes (liaising with recruiting neurologists and CRN research support workers). We will consider the need to include additional neurology clinics for recruitment. If there are issues with people agreeing to take part, we will consider and attempt to address factors influencing this decision, such as travel, provision/perception of the control vs study intervention and we will monitor closely how the trial is being explained and represented to potential participants. We will report the results of our internal pilot to the HTA at the end of month 15. If the progression criteria are not met, in consultation with the HTA we will consider if the trial should stop or if additional measures can be put in place to allow the trial to continue.

10 SELECTION OF PARTICPANTS

10.1 INCLUSION CRITERIA

1. New or returning patients presenting to participating outpatient neurology clinics and neurology inpatients.
2. The patient has a "clinically definite" diagnosis of FMD according to the Gupta and Lang diagnostic classification criteria [1].
3. Age 18 or over.
4. Diagnostic investigations have come to an end.
5. The patient is accepting of the intervention.
6. Motor symptoms must be sufficient to cause significant distress or impairment in social, occupational or other important areas of functioning (subjectively described by the patient), independent of other comorbidities.

10.2 EXCLUSION CRITERIA

1. The recruiting neurologist deems the patient to have severe psychiatric comorbidity, including factitious disorder, self-harm, anxiety and depression, which would interfere with the patient's ability to participate in physiotherapy.**
2. The patient has an organic diagnosis which explains the majority of their symptoms or disability.
3. The patient has pain, fatigue or dissociative seizures that would interfere with their ability to engage in the trial physiotherapy intervention.
4. Disability to the extent that the patient requires assistance for toileting.
5. The patient is unable to attend 9 sessions of physiotherapy over a 3 week period, within 6 weeks of initial neurology consultation.
6. Ongoing unresolved compensation claim or litigation.
7. The patient has no fixed address or is seeking rehousing through their council for disability access reasons.
8. Unable to understand English sufficiently to complete questionnaires.
9. The patient has a documented learning disability that prevents them from answering questionnaires independently.
10. The patient lacks capacity to give consent.

** The decision to exclude a patient due to psychiatric comorbidity is a clinical decision made by the neurologist, rather than a decision based on a screening tool or questionnaire. We believe that no single screening tool or questionnaire would serve this purpose. Additionally, there is insufficient data on which to base cut-off scores to exclude patients on any particular questionnaire.

11 STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

11.1 PARTICIPANT IDENTIFICATION

Participants will be recruited from outpatient neurology clinics and inpatients due to be discharged at participating centres, by a consultant neurologist signed up to the trial. Patients with a "clinically definite" diagnosis of FMD will be screened for eligibility. A paper

based screening log will be completed by the neurologist for all screened patients. Aggregated anonymised data from the screening logs for each site will be uploaded to the trial database on a regular basis, approximately every month.

11.2 INFORMED CONSENT PROCEDURE

Patients identified as eligible and consenting to be contacted by the research team will be approached following their neurology appointment. The principal investigator (PI), or a person delegated by the PI will provide an adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. If the person is eligible and interested in taking part, an appointment will be arranged for a face-to-face meeting to complete the consent process. Potential participants will be given time to consider fully the likely implications of the research before making a decision. Potential participants will not be rushed into decisions and shall be given the opportunity to have time to discuss their decision with family and friends beforehand if they wish. During the consent meeting, the PI or designee will answer any questions the patient may have about the study before obtaining written informed consent and will explain to the participants that they are under no obligation to enter the trial and can withdraw at any time during the trial, without having to give a reason. The PI or designee will record when the participant information sheet (PIS) has been given to the participant. No research procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into trial. A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes. Once consent has been obtained, the participant will be asked to complete the baseline assessments. The PI or designee will complete the baseline case report form and pass the details of the consented participant to the Trial Manager for randomisation. If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and participants will be re-consented as appropriate.

11.3 SCREENING PERIOD

Potential participants are screened against the eligibility criteria; no additional screening assessments are conducted.

The baseline visit will occur within 8 weeks of the screening visit (neurology outpatient appointment or inpatient consultation). Randomisation is the last procedure to be completed at baseline.

Screening failures (i.e. participants who do not meet eligibility criteria at time of screening) may be eligible for rescreening.

11.4 RANDOMISATION PROCEDURES

The Trial Manager will perform the randomisation procedure after consent and baseline data collection are completed.

Randomisation will be conducted by the Trial Manager using a remote computerised web-based application, Sealed Envelope, provided by Priment CTU. Randomisation will occur at the level of the patient, stratified by site. Block randomisation with random block sizes will be used to ensure even allocation of intervention and control participants across sites.

The Trial Manager will not be blinded to treatment allocation, and therefore will be able to contact the participant to inform them of their trial arm allocation and will also inform the study neurologist of the treatment allocation. For intervention-allocated participants, the Trial Manager will notify the study physiotherapist, who will arrange treatment. If a participant has been randomised to the control arm of the trial, the trial neurologist will refer the patient to the local community physiotherapy service, enclosing the participant's neurology consultation letter explaining the diagnosis.

The researchers collecting data, statisticians and health economists will remain blind to group allocations. The neurologists will not be blinded.

11.5 UNBLINDING

The study neurologists and physiotherapists involved in the participant's clinical care are not blind to treatment allocation.

In case of a medical emergency, participants will be able to disclose to the treating physician (e.g. GP) what treatment they received without unblinding the researchers; as such, an emergency unblinding system is not required for this study.

Blinding will be tested by asking the research assistants collecting data to record when they think that allocation has been revealed and record the group to which they thought patients had been allocated.

Assessors will minimise the risk of becoming unblinded by reminding participants at each stage that they must not discuss their intervention with their assessor. If an assessor does become unblinded we will make a note of this and ask an alternative assessor to complete future outcome measures for this participant.

11.6 BASELINE ASSESSMENTS

The participant will meet the PI or designee to complete the informed consent process. After giving consent, the participant will complete the CRF and assessment questionnaires with help from the PI or designee. The data collected at baseline assessment are:

11.6.1 DEMOGRAPHIC AND CLINICAL DATA

This will be obtained from both the medical notes and from the participant. Demographic data includes name, date of birth, gender, NHS number, etc. Clinical data includes symptom phenomenology, symptom duration, past medical history, current medications, etc.

11.6.2 CLINICAL ASSESSMENTS (QUESTIONNAIRES)

After completing the demographic and baseline data, the participant will be provided with a booklet of questionnaires.

The baseline clinical assessments (questionnaires) are:

1. Short Form 36 [33]
2. Functional Mobility Scale [22]
3. Revised Illness Perception Questionnaire [26]
4. Hospital Anxiety & Depression Scale [27]
5. Client Service Receipt Inventory [21]
6. EQ-5D-5L [28]
7. Work Productivity & Impairment Questionnaire [34]
8. Fatigue State (single question) [35]
9. Extended PHQ-15 [32]
10. Confidence in correctness of diagnosis of FMD [24]

11.7 TREATMENT PROCEDURES

11.7.1 INTERVENTION CONDITION

The health technology being assessed is a novel physiotherapy treatment protocol for FMD (Specialist Physiotherapy) involving symptom education, movement retraining with redirection of motor attention, and developing a long term self-management plan. The intervention is delivered over 9 sessions within a 3 week period, plus a 3 month follow up session. There are usually 2 sessions on most days (separated by a lunch break); however, flexibility is built into the arrangement of sessions over the 3 weeks to allow for lifestyle factors of the participant such as work and childcare and to accommodate the requirements of the physiotherapy service/physiotherapist. The intervention is described in a manual and the study physiotherapists receive comprehensive training to deliver the intervention.

The intervention is guided by a workbook that is completed by both the patient and physiotherapist during sessions and the patient may be asked to complete short "homework" activities in between sessions. The intervention starts with taking a full history from the patient and performing a physical assessment. This is followed by education on FMD according to a biopsychosocial aetiological model biased towards physical factors [14]. The patient and physiotherapist collaboratively devise a formulation to theorise how the patient developed their movement problem using the biopsychosocial aetiological model as a framework and incorporate the history obtained from the patient [14]. This takes into account triggering events, comorbidity, psychological factors (such as panic at onset), self-focused attention disrupting normal movement, and unhelpful reinforcement of symptomatic movement patterns. Next, strategies are developed and practiced to normalise movement, which have been described in detail elsewhere [38]. The important factor of the strategies is that they redirect the patient's attention (distraction) and encourage automatic movement. They are put into practice over the remaining sessions

(while practising activities such as walking, transferring, getting on and off the floor, drinking from a cup, etc). A long term self-management plan is completed in the workbook in the final sessions. Fatigue, pain, and memory and concentration problems are addressed with information and management strategies if they are relevant to the patient. The 3 month follow up session is an opportunity to review and update the self-management plan, as well as to provide encouragement and reassurance.

The study physiotherapist will record the number and composition of each intervention physiotherapy session in a log based on the TIDieR checklist [39] (this is a template used for intervention description and replication, an extension of the CONSORT statement). The intervention differs from standard physiotherapy as there is a large emphasis on education and self-management, but more importantly the movement retraining aims to redirect the patient's attention (distract) away from their body, whereas standard physiotherapy tends to encourage the patient to think about their body (which exacerbates FMD).

Study physiotherapists delivering the intervention will undergo a training programme over 5 consecutive days and will need to demonstrate competency in delivering the intervention prior to treating study participants. Competency will be assessed by the CI, using a competency checklist, marked during observation of clinical sessions and role-play.

11.7.2 CONTROL CONDITION

The control arm of the trial is "treatment as usual", which we will standardise as a referral to community physiotherapy appropriate for neurological patients. The referral letter will come from the diagnosing neurologist, after the initial consultation and confirmation from the Trial Manager that the patient has been allocated to the control condition. The referral letter will contain standardised information about the diagnosis of FMD. We will monitor the content of the control physiotherapy arm via participant report.

As previously described, there are no formal guidelines for physiotherapy for FMD. Therefore, the treatment received by the control participants will be variable. Based on our feasibility study, we found that most physiotherapists provide a combination of gait retraining, stair practice, balance, non-specific cardiovascular exercise, specific strengthening exercises, stretching, and provision of walking aids or splints. The frequency and number of physiotherapy sessions provided by community therapy services will differ between centres, according to local policies. In addition, some trial participants may be offered treatment from occupational therapy or clinical psychology, although in our feasibility study we found that this was rare. Additional treatments such as these will be monitored and recorded at the 6 month and 12 month data collection through specific questionnaires (CSRI) and the CRF.

11.7.3 BOTH GROUPS

Study participants in both arms of the trial will be followed up by their neurologist at least once within 12 months of their initial neurology consultation (which is part of standard NHS care).

11.8 SUBSEQUENT ASSESSMENTS

Subsequent assessments will be conducted remotely via post, telephone, or secure internet application, depending on the participant's preference. The study research assistants will conduct the reassessments at 6 and 12 months post randomisation. The baseline clinical assessments listed above will be repeated, with the addition of a clinical global impression scale of improvement.

11.8.1 SIX MONTH AND 12 MONTH ASSESSMENTS:

1. Short Form 36 (SF36), the Physical Function domain (SF36-PF) of the SF36 is the primary outcome measure [33]
2. Functional Mobility Scale [22]
3. Revised Illness Perception Questionnaire [26]
4. Hospital Anxiety & Depression Scale [27]
5. Client Service Receipt Inventory [21]
6. EQ-5D-5L [28]
7. Work Productivity & Impairment Questionnaire [34]
8. Clinical Global Impression Scale of Improvement, patient rated (CGI-I)
9. Fatigue State (single question 5-point scale based on EQ-5D-5L) [35].
10. Confidence in correctness of diagnosis of FMD (10 point scale) [24]
11. Adverse events screen

11.8.2 ASSESSMENT OF TREATMENT FIDELITY & SATIFACTION WITH TREATMENT

In addition to the clinical assessments, we will monitor the provision of physiotherapy in both groups by participant report with a structured telephone survey conducted by the Trial Manager. Participants will be surveyed as soon as possible after their final scheduled physiotherapy session. The survey will explore the content, number and length of physiotherapy sessions. The data will be used as part of the assessment of intervention fidelity and to determine participant satisfaction with their allocated treatment. The surveys will be conducted by the Trial Manager to prevent unblinding of the research assistants.

11.8.3 HOSPITAL EPISODE STATISTICS (NHS DIGITAL DATA)

We will also obtain official NHS data on the number of hospital contacts (outpatient, inpatient and A&E) made by each participant in the 12 months prior to treatment and the 12 months post randomisation. These data are obtained separately from NHS England and NHS Scotland. The English data are supplied by NHS Digital and are called Hospital Episode Statistics (HES) [31,39]. The Scottish data are supplied by the Electronic Data Research and Innovation Service and we will refer to it as Information Services Division (ISD) data [32]. The Trial Manager will request these data to ensure the statistician and health economist

are not unblinded. Personal identifiable participant data will be transferred securely into the UCL Data Safe Haven.

11.9 FLOWCHART OF STUDY ASSESSMENTS

Study Procedures		Face-to-face assessment	Telephone or post contact		
		Screening & Baseline Assessment	**6 Months**	**Assessment of fidelity & feedback ***	**12 Months**
Informed consent		✓			
CRF	Inclusion/exclusion criteria	✓			
	Medical history	✓			
	Demographics	✓			
	Clinical characteristics	✓			
Assessment	Short Form 36	✓	✓		✓
	Functional Mobility Scale	✓	✓		✓
	Revised Illness Perception Qu.	✓	✓		✓
	Hospital Anxiety & Depression Scale	✓	✓		✓
	Client Service Receipt Inventory	✓	✓		✓
	EQ-5D-5L	✓	✓		✓
	Work Productivity & Impairment Qu.	✓	✓		✓
	Clinical Global Impression Scale (CGI-I)		✓	✓	✓
	Fatigue State	✓	✓	✓	✓
	Extended Patient Health Questionnaire-15	✓			
	Confidence in correctness of diagnosis	✓	✓		✓
Randomisation		✓			
Adverse events screen			✓	✓	✓
Satisfaction with intervention Qu.				✓	
Description of intervention telephone call				✓	
Trial Manager obtains HES data from NHS digital					

11.10 METHODS

11.10.1 LABORATORY PROCEDURES

Not applicable

11.11 DEFINITION OF END OF TRIAL

The end of the trial will be when the last assessment of the last participant in the trial is completed. The anticipated end of trial date is 30 April 2021.

11.12 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND 'STOPPING RULES'

In consenting to the trial, participants are consenting to trial treatments, trial follow up and data collection. However, an individual participant may stop treatment early or be stopped early for any one of the following reasons:

- Intercurrent illness that prevents further protocol treatment

- Any change in the participant's condition that is in the investigator's opinion justifies the discontinuation of treatment
- Withdrawal of consent from the participant

As participation in the trial is entirely voluntary, the participant may choose to discontinue participation at any time without penalties or loss of benefits to which they may be entitled. Although not obliged to give a reason for discontinuing their participation, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights. Participants who discontinue study participation, for any of the above reasons, should remain in the study for the purpose of follow up and data analysis.

If a participant chooses to discontinue they should be continued to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. However if the participant confirms they do not wish to participate in the scheduled follow up data collection then data that has already been collected should be kept and analysed (unless participants specifically request this data to be destroyed) according to the ITT principle for all participants who stop follow up early.

Participants who stop the trial follow up early will not be replaced.

The trial may be stopped early if the go criteria to progress from the internal pilot study are not met. If the trial is prematurely stopped, all planned treatments will be continued.

The DMEC will consider stopping the trial based on serious adverse events.

Participants who fail to return posted outcome measures will be followed up by telephone, text message or email. Unless the participant withdraws from the study, the participants will receive 3 telephone reminders and the research worker will offer to collect outcome measures over the phone. The outcome measures will be collected in an order of priority, starting with the primary outcome (order of priority: SF36, CGI-I, EQ-5D-5L, Functional Mobility Scale, Hospital Anxiety and Depression Scale, Fatigue State, CSRI, Revised Illness Perception Questionnaire, Work Productivity and Impairment Questionnaire, Confidence in correctness of diagnosis).

11.13 CONCOMITANT MEDICATION/TREATMENT

Participants will not be restricted from receiving concurrent treatment and therapies, such as psychological therapy.

Based on the research team's experience, it is expected that only a minority of patients meeting the eligibility criteria will receive additional interventions such as psychology and occupational therapy. Randomisation should ensure that those who do receive additional treatment will be evenly distributed between the arms of the trial. Receipt of additional treatment will be monitored and their impact will be assessed in a sensitivity analysis.

11.14 POST-TRIAL ARRANGEMENTS

If deemed clinically appropriate, participants in either arm of the trial who continue to experience disability following physiotherapy will be referred to further NHS specialist treatment by their neurologist.

The approach of starting with a brief intervention and increasing the complexity of treatment as necessary has been advocated by Health Improvement Scotland in a document titled "Stepped care for functional neurological symptoms" [40]. Escalation of treatment may include specialist psychology/psychiatry, multidisciplinary intervention (involvement of occupational therapy and/or speech and language therapy), and inpatient rehabilitation.

12 DATA MANAGEMENT

All aspects of data management of the study will comply with the UK Data Protection Act 1998 and any amended Data Protection regulations, Priment SOPs and GCP.

12.1 CONFIDENTIALITY

The Case Report Forms (CRFs) will not bear the participant's name. The participant's initials, date of birth and trial identification number will be used for identification. Any personal data collected will be managed according to Priment SOP Managing Personal Data.

12.2 DATA COLLECTION TOOLS

The data collection tools will be created according to Priment SOP Development, Review and Approval of Case Report Forms.

12.3 TRIAL DATABASE

The CRFs will be entered into a web-based clinical data management system, Red Pill, provided by Sealed Envelope through Priment. Sealed Envelope has been assessed by Priment to ensure that adequate processes are in place and are being followed for quality management, software development and security. Database services and support will be delivered through a contract signed by Sealed Envelope and UCL.

Priment SOPs Validating Sealed Envelope Systems and Change Control for Sealed Envelope Systems will be followed to set up and manage changes to the trial database.

At the end of the trial, prior to analysis, Priment SOP Database Lock, Unlock and Closure will be followed.

12.4 DATA COLLECTION AND HANDLING

All data will be collected and handled in accordance with Priment SOP Data Handling.

The Chief Investigator or Principal Investigator will ensure the accuracy of all data entered in the CRFs. The Trial Manager will also monitor accuracy of data entry. The delegation log will

identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

12.5 DATA OWNERSHIP

At the end of the trial, the data belongs to St George's, University of London.

13 RECORD KEEPING AND ARCHIVING

Archiving will be authorised by the Sponsor following submission of the end of study report.

The trial essential documents along with the trial database will be archived in accordance with the Sponsor SOP JREOSOP0016. The agreed archiving period for this trial will be 10 years.

Each PI at any participating site will archive the trial essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site agreement. All essential documents will be archived for a minimum of 10 years after completion of trial. It will be archived in line with the sponsor's SOP.

Destruction of essential documents will require authorisation from the Sponsor.

14 STATISTICAL CONSIDERATIONS

Dr Louise Marston is the trial statistician who will be responsible for all statistical aspects of the trial from design through to analysis and dissemination.

14.1 STATISTICAL ANALYSES

14.1.1 SUMMARY OF BASELINE DATA AND FLOW OF PARTICIPANTS

Data will be reported in accordance with CONSORT guidelines [41]. We will construct a CONSORT diagram to describe the flow of subjects through the study. We will present baseline means and standard deviations or median and interquartile ranges of continuous measures as appropriate, and frequencies and percentages of categorical measures. An intention to treat analysis will be conducted after the database is locked following collection of final 12 month follow up data.

14.1.2 PRIMARY OUTCOME ANALYSIS

The primary outcome is the Physical Function domain of the Short Form 36 Questionnaire (SF36-PF). This will be analysed using random effects modelling, using therapist as the random effect (individuals for those in the TAU group), controlling for baseline SF36-PF.

14.1.3 SECONDARY OUTCOME ANALYSIS

The CGI-I scale will be collapsed into two groups, good outcome and poor outcome. Good outcome will be defined as ratings of "much improved" or "improved" and poor outcome will be defined as rating of "same", "worse", or "much worse". This will be analysed using random effects logistic regression. Other clinical secondary outcomes will be analysed as for the primary outcome.

For the HES/ISD data, we will report descriptive statistics for each service type (outpatient, A&E, inpatient) separately. Suitable descriptive statistics and statistical tests will be selected for each service type depending on the distribution of the data (i.e. non parametric tests for highly skewed data). We will include an analysis using general linear models (GLM) and appropriate family and log links to account for the distribution of the data. The GLM models will be used to calculate differences in service use between trial arms, adjusting for baseline service use. The total cost for each service use type will be reported as part of the health economic analysis

14.1.4 SENSITIVITY AND OTHER PLANNED ANALYSES

We will perform sensitivity analyses looking at the effect of missing data, additional interventions received (e.g. psychology) and dose-response relationship for the control and intervention conditions.

An exploratory analysis of prognostic indicators will be performed. This will use random effects logistic regression modeling to determine predictors of a good or bad outcome from baseline demographic and clinical characteristics. Outcome will be determined by a self-rating of "improved" or "much improved" on the CGI-I scale and a 10 point increase in SF36-PF score. This analysis will be indicative, and any factors which appear to be associated with the outcome will need further investigation in a study that is powered for the purpose.

14.2 INTERIM ANALYSIS

No interim statistical analyses are planned.

14.3 OTHER STATISTICAL CONSIDERATIONS

Not applicable.

15 QUALITATIVE METHODS

We will undertake a qualitative study with the trial intervention physiotherapists to investigate their experiences of delivering the trial intervention. The trial physiotherapists will be invited to take part in a one-to-one interview. The aim is to gather information for implementation purposes and to help improve the overall impact of the study.

The qualitative study will be conducted by a student from the University of Plymouth, as part of a Masters in Science degree. They will be supported by Professor Jonathan Marsden,

a named trial co-investigator and a university appointed supervisor, experienced in qualitative research methods.

15.1 AIMS AND OBJECTIVES

Research question:

What are the experiences of physiotherapists delivering the Physio4FMD RCT protocol intervention and how could the intervention translate into routine clinical practice?

Aims:

- To understand how delivering the protocol is different from usual care.
- To understand which aspects of the protocol are felt to be most important.
- To understand the practicalities of delivering the protocol intervention outside of a clinical trial.
- To understand the selectivity of appropriate patients for the intervention outside of a clinical trial.

Objectives:

To use Thematic Analysis to synthesise key themes among physiotherapists that delivered the Physio4FMD protocol regarding:

- Their experiences of delivering the protocol.
- Barriers and facilitators to delivering the intervention.
- How the protocol may translate outside of a clinical trial.

15.2 SELECTION OF PARTICIPANTS

We will approach physiotherapists who are involved in the delivery of the protocolised trial intervention. To be eligible to take part, the physiotherapists must have received the 5-day intervention training and treated a minimum of two intervention participants.

All eligible trial physiotherapists will be invited to participate.

15.3 STUDY PROCEDURES

15.3.1 PARTICIPANT IDENTIFICATION

The researcher will invite physiotherapists to participate in the study by email. The physiotherapists will be informed that their participation is voluntary and they do not have to provide a reason for non-participation. A copy of the physiotherapist participant information sheet (PIS) will be attached to this email. Should the physiotherapist have any questions they will be directed to contact the researcher. If a physiotherapist is interested in taking part in the study, they will be provided a copy of the electronic Informed Consent Form (eICF) by email and a suitable time will be arranged between the researcher and physiotherapist by MS Teams/Zoom to provide consent and conduct the interview.

15.3.2 INFORMED CONSENT

To facilitate the remote consent process, the consent form will be converted into a PDF fillable form. The online platform DocuSign will be used to collect electronic signatures.

Whilst on MS Teams/Zoom and before conducting the interview, the researcher will further discuss the study and answer any questions that the physiotherapist may have. If the physiotherapist is still willing to participate, the researcher will ask the physiotherapist to sign the eICF and return to the researcher by email. The researcher will then countersign the eICF and return a fully signed copy to the physiotherapist by email, instructing them to keep a copy for themselves as well as filing a copy in the Investigator Site File at their respective participating site.

15.3.3 INTERVIEWS

After consent has taken place, the interview will commence at the discretion of the physiotherapist. The interview is expected to last 60 minutes.

The interview will be conducted in accordance with an approved semi-structured interview schedule. The physiotherapist can request to stop the interview at any time and they can decline to answer any questions that they do not wish to answer, without having to give a reason.

The interview will be audio-recorded via the MS Teams/Zoom platforms.

The interview will be transcribed by the researcher after it has taken place. Once the transcripts are final, the audio-recording will be destroyed.

15.3.4 CONFIDENTIALITY

Each physiotherapist who consents to take part in the study will be assigned a unique study code to maintain confidentiality. Only the researcher conducting the interview will know which physiotherapists have taken part, all other research staff (Chief Investigator, Trial Manager etc.) will only know the participants by their study code. Audio-recordings will be stored on a secure password protected computer and will only be accessible by the researcher conducting the interviews. The recordings will be destroyed once the transcripts have been finalised.

15.4 ASSESSMENT AND MANAGEMENT OF RISK

There is minimal risk involved in conducting virtual one-to-one interviews with physiotherapy staff. The independence of the researcher conducting the interviews from the main RCT will reduce the influence of the interviewer on how the physiotherapists respond to the questions. To further ensure their responses are not biased to providing positive feedback only, the Chief Investigator will not be notified of who has taken part in the study, and will not be able to identify individuals in the transcripts as these will be pseudo-anonymised.

16 ECONOMIC EVALUATION

The aims of the health economic evaluation will be twofold:

1. To estimate the cost impact of the Specialist Physiotherapy protocol compared to treatment as usual for FMD over 12 months, firstly from a health and social care cost perspective and secondly from a societal perspective.

2. Calculation of Quality Adjusted Life Years (QALYs) over 12 months from responses to the EQ-5D-5L and calculated as the area under the curve adjusting for baseline [34]. This will be used to calculate the mean incremental cost per QALY gained with the specialist physiotherapy protocol compared to treatment as usual over 12 months. Bootstrapping will be used to construct confidence intervals, cost-effectiveness planes and cost-effectiveness acceptability curves. Sensitivity analyses will be conducted to test the impact of any assumptions made as part of the analysis.

The primary health economic analysis will be from a health and social care cost perspective with a secondary analysis to account for the impact on employment from a societal perspective. Similar to the analysis of the primary outcome we will use random effects modelling for the therapist effect.

The trial team have previously developed and tested a version of the CSRI in patients with FMD as part of our feasibility study. An adapted version of the CSRI, informed by our experience of using the questionnaire in the feasibility trial, will be used to collect resource use and employment information. The WPAI-SHP will be used to calculate the cost impact of improved engagement with employment as a result of being randomised to specialist physiotherapy. Productivity will be costed using the human capital approach. Other resource use will be costed using nationally published sources including the Personal and Social Services Research Unit [42], British National Formulary [43] and National Reference Costs [44].

HES/ISD data will be used to validate the results of the analysis of secondary care service use. The data will include information on Healthcare Resource Groups (HRGs) for inpatient HES data and diagnostic and procedural codes for all other data and will be costed using the National Reference Costs [44]. The CSRI analysis will be validated with the HES/ISD data by (a) applying more specific costs based on reason of attendance; (b) checking the reliability of patient reporting; and (c) investigating the implications for the cost-effectiveness analysis including HES/ISD data for patients with missing data on the CSRI due to incomplete data on the CSRI or loss to follow-up.

17 NAME OF COMMITTEES INVOLVED IN TRIAL

17.1 TRIAL MANAGEMENT GROUP

A Trial Management Group (consisting of the co-applicants, Trial Manager, and 2 previous service users (PPI representatives) will meet up to 9 times in a year (making use of teleconferencing), to ensure the safe and efficient conduct of the trial in all regions and that the protocol is adhered to.

17.2 TRIAL STEERING COMMITTEE (TSC)

The TSC will be set up and meet six monthly. It will have an independent chair and it will include PPI representation. The committee will monitor progress and scientific conduct of the trial to ensure that it is being conducted in accordance with the principles of GCP. The Trial Steering Committee will agree the trial protocol and any protocol amendments and provide advice to the Investigators on all aspects of the trial. Decisions about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the Trial Steering Committee.

17.3 DATA MONITORING AND ETHICS COMMITTEE (DMEC)

A Data Monitoring and Ethics Committee (DMEC) will be set up, following HTA requirements for appointments to the committee. The DMEC will meet 6 monthly or more frequently as required and review data and any reported adverse events/safety related issues. The DMEC will advise the Trial Steering Committee.

18 RECORDING AND REPORTING OF ADVERSE EVENTS AND REACTIONS

18.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant whether it is considered to be related to the intervention or not, that includes a clinical sign, symptom, or condition and /or an observation of a near incident. (This does not include pre-existing conditions recorded as such at baseline; continuous persistent disease or a symptom present at baseline that worsens following administration of trial intervention.
Serious Adverse Event (SAE)	Any untoward occurrence that: • results in death, • is life-threatening,

	• requires hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect • is otherwise considered medically significant by the investigator
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any SAE that is deemed to be • Related to the trial intervention AND • Unexpected (not listed in the protocol as an expected side effect of the intervention)

For the purposes of the trial, a transitory exacerbation of chronic pain or fatigue following physiotherapy intervention that resolves without the need for additional interventions will not be considered an adverse event.

18.2 EXPECTED SIDE EFFECTS

If a patient experiences an adverse event that is not listed in this protocol then this should be classed as unexpected (see section 18.4 B).

Expected side effects of the intervention include:

- Some musculoskeletal discomfort following physiotherapy sessions
- Physical tiredness
- Mental tiredness
- Exacerbation of pre-existing chronic pain
- Exacerbation of pre-existing chronic fatigue

18.3 RECORDING ADVERSE EVENTS

All adverse events will be recorded in the medical records, CRFs or other designated place following consent. All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

All adverse events will be recorded until the final 12 month assessment. A record of all AEs whether related or unrelated to the treatment will also be kept in the CRF and the AE Log.

The 6 and 12 month assessment forms will ask open ended questions about adverse events. Participants will be instructed to contact the principal investigator at the site to report serious adverse events.

18.4 ASSESMENTS OF ADVERSE EVENTS

Each serious adverse event will be assessed to determine if the event is related to the intervention and if the event is expected.

A. RELATED EVENTS

The assessment of the relationship between adverse events and the administration of the intervention is a decision based on all available information at the time of the completion of the case report form. If the event is a result of the administration of any of the research procedures then it will be classed as related.

B. EXPECTED EVENTS

If the event has been listed in the protocol (section 18.2) as an expected side effect of the intervention then the event will be classed as expected. If the event is not listed then it will be classed as unexpected.

18.5 PROCEDURES FOR REPORTING SERIOUS ADVERSE EVENTS

Any serious adverse events which are deemed related and unexpected are classed as SUSARs and will be reported to the ethics committee that approved the trial, the Sponsor, and to Priment. The reporting of SUSARs to the ethics committee will be completed according to Priment non-CTIMP safety management SOP and HRA guidelines, using the SAE report form for research other than CTIMPs (non-CTIMPs) published on the HRA website.

The Chief Investigator (or their delegate) is responsible for reporting SUSARs to the ethics committee that approved the study within 15 calendar days of becoming aware of the event.

Once information about an adverse event has been received by a member of staff working on the study, the information will be reviewed to identify any SAEs or SUSARs. If an event meets the definition of a SAE or SUSAR, the CI and Priment must be notified within 24 hours (normal office hours) of becoming aware of the event. The Principal Investigator at any participating site will complete the SAE form which will be emailed to the CI and to Priment Pharmacovigilance Coordinator on primentsafetyreport@ucl.ac.uk. The Principal Investigator will respond to any SAE queries raised by the CI or by Priment as soon as possible.

Follow up reports must continually be completed within acceptable time-frames and sent as detailed above until the reportable event is considered resolved.

18.6 THE TYPE AND DURATION OF THE FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS

In the event that a participant suffers from a SAE, we will advise the participant to contact their GP immediately and follow up with the participant until a resolution or stabilisation is reached.

Adverse events will be recorded and reported until the final study assessment at 12 months post randomisation.

18.7 ANNUAL PROGRESS REPORTS

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The Chief Investigator will prepare the APR.

18.8 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken, the CI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to REC of the measures taken and the circumstances giving rise to those measures.

18.9 NOTIFICATION OF SERIOUS BREACHES TO GCP AND/OR THE PROTOCOL

A "serious breach" is a breach which is likely to affect to a significant degree:

(a) The safety or physical or mental integrity of the participants of the trial; or

(b) The scientific value of the trial.

The Sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of:

(a) The conditions and principles of GCP in connection with that trial; or

(b) The protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The Sponsor's SOP on 'serious breaches' will be followed.

19 MONITORING AND INSPECTION

A monitoring plan will be established for the trial based on the risk assessment. The trial will be monitored with the agreed plan.

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

20 ETHICS AND REGULATORY REQUIREMENTS

The Sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory bodies, prior to any participant recruitment. The protocol and all agreed

substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before the site can enrol participants into the trial, the Chief Investigator/ Principal Investigator or designee must apply for NHS permission from their Trust Research & Development (R&D) office and be granted written permission. It is the responsibility of the Chief Investigator/ Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participants (see section for reporting urgent safety measures).

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the main REC within 1 year after the end of the trial.

20.1 PUBLIC AND PATIENT INVOLVEMENT (PPI)

The study protocol was developed in collaboration with PPI representatives from the early planning stages. The initial PPI focus was to ensure the research question and intervention is meaningful to patients and relevant to their needs; to ensure the methodology is acceptable; and to ensure we are measuring meaningful outcomes.

The aims for PPI during the conduct of the trial is to support and provide advice on the conduct and management of the trial; to provide input into interpretation of results and to support and oversee dissemination of results to relevant stakeholders.

The main forum for PPI will be our service user representatives on our Trial Management Group. We will also have service users input on the Trial Steering Committee. The role of the PPI representatives will be to input into development of trial materials (information sheets, educational materials, consent forms, and letter templates); input into project management and issues arising that are discussed in the Trial Management/Steering Committee meetings; input into analysis of the results to consider what is a meaningful change for patients; support with dissemination by helping to identify avenues of dissemination and present results. The trial budget includes funds for training, reimbursement of travel and reimbursement of time for the PPI plans.

The trial team will continue to engage with the patient support charities FNDHope.org and FNDAction.org.uk. These are charities setup and run by people with FMD. Both groups have agreed to provide on-going support for our research and help with dissemination.

21 FINANCE

This study is funded for 43 months by an NIHR HTA grant.

22 INSURANCE

St George's University of London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that St George's has been negligent. This includes negligence in the writing of the protocol, or selection of trial resources.

Where the Trial is conducted in a hospital, the hospital has a duty of care to participants. St George's University of London will not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to St George's University of London, upon request.

Participants may be able to claim compensation for injury caused by participation in this Trial without the need to prove negligence on the part of St George's University of London or another party.

If a participant indicates that they wish to make a claim for compensation, this needs to be brought to the attention of St George's University of London immediately.

Failure to alert St George's University of London without delay and to comply with requests for information by the Sponsor or any designated Agents may lead to a lack of insurance cover for the incident.

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate.

23 PUBLICATION POLICY

Publication: "Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations."

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a

firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

23.1 BEFORE THE OFFICIAL COMPLETION OF THE TRIAL

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the Steering Committee shall have the final say.

Exempt from this requirement are student theses that can be submitted for confidential evaluation but are subject to embargo for a period not shorter than the anticipated remaining duration of the trial.

23.2 UP TO 180 DAYS AFTER THE OFFICIAL COMPLETION OF THE TRIAL

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

- The Chief Investigator shall be senior and corresponding author of the Main Publication.
- Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.
- Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.
- Members of the Steering Group shall only be acknowledged as co-authors if they contributed in other capacities as well.
- If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

23.3 BEYOND 180 DAYS AFTER THE OFFICIAL COMPLETION OF THE TRIAL

After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor's

reasonable comments shall be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

24 STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the UK policy framework for health and social care research, GCP and the applicable regulatory requirement(s).

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