A randomised controlled trial of Specialist Physiotherapy for Functional Motor Disorder (Physio4FMD)

Statistical & Health Economic Analysis Plan

Version History Log

Version	Date	Changes
0.1	30/03/2020	
0.2	06/04/2020	Added Health Service Use outcomes
0.3	14/04/2020	Added queries for the Team. Minor edits
0.4	15/05/20	Added Health Economics Section
0.5.1	17/11/2020	Added "Assessment of Intervention Fidelity & Satisfaction" Section, modified "Sensitivity analysis" Section + minor edits
0.6	14/01/2021	Edited sensitivity analyses section + minor edits
0.7	18/05/2021	Added CACE sensitivity analysis + dose/response analysis
0.8	11/06/2021	Minor edits

SHEAP Authorisation

Author	
Name:	Dr Federico Ricciardi
Role:	Trial statistician
Signature:	
Date:	

Approver	
Name:	Dr Louise Marston
Role:	Lead statistician
Signature:	
Date:	

Author	
Name:	Marie Le Novere
Role:	Trial health economist
Signature:	
Date:	

Approver	
Name:	Rachael Hunter
Role:	Lead health economist
Signature:	
Date:	

Approver	
Name:	Dr Glenn Nielsen
Role:	Chief investigator
Signature:	
Date:	

Contents

1. Study Summary

For full details see the protocol (version 7.0, xx/05/2021).

Title	A randomised controlled trial of Specialist Physiotherapy for Functional Motor Disorder.
Short title	Physio4FMD
Chief Investigator	Dr Glenn Nielsen
Statisticians	Louise Marston & Federico Ricciardi
Health economist	Rachael Hunter & Marie Le Novere
Design	Pragmatic, multi-centre, single-blind, parallel group, randomised controlled trial in adults with functional motor disorder (FMD).
Primary objective	To evaluate the effectiveness of Specialist Physiotherapy compared to treatment as usual (TAU) in reducing disability at 12 months.
Primary Outcome	Physical Function domain of the Short Form 36 questionnaire at 12 months' post randomisation
Population	<u>Inclusion criteria</u> 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. 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. <u>Exclusion criteria</u> 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.

Sample size Minimum of 264 (132 per group); maximum of 300 (150 per group).

Randomisation Online randomisation (with blocking with random block sizes) is used to randomise at the level the patient and stratified by site.

Trial registration no. ISRCTN56136713

2. Introduction

2.1 Purpose and scope of the statistical analysis plan

This document describes the main statistical analyses to be applied to the data from Physio4FMD Trial. This Statistical & Health Economic Analysis Plan (SHEAP) was written by Federico Ricciardi (FM), Louise Marston (LM) Caroline Clarke (CC), Rachael Hunter (RH) and Marie Le Novere (MLN).

2.2 Analysis organisation

Data will be analysed blind to allocation by statisticians and health economists. The primary analysis will be performed independently by two statisticians (FR and LM) to ensure its accuracy.

2.3 Data checking

Before database lock and analysis, basic checks will be performed to check the quality of the data. Incomplete or inconsistent data include:

- Missing data
- Data outside expected range
- Other inconsistencies between variables e.g. in the dates the questionnaires were completed

If any inconsistencies are found, the corresponding values will be double checked with the researchers and corrected if necessary. All inconsistencies will be documented by the trial statistician, health economist. All changes will be documented by the trial manager and given to the trial statistician and health economist.

3 Trial Objectives (from Protocol)

3.1 Primary objective

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.

3.2 Secondary objectives

The secondary objectives are to evaluate:

a) 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) from England and Information Services Division data from Scotland;
b) 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);
c) 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;
d) 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 and expressed via the physical and mental health domains;
e) The participant's perception of change at 6 and 12 months' post randomisation using the Clinical Global Impression Scale of Improvement (CGI-I);
f) 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;
g) 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;
h) The cost-effectiveness of Specialist Physiotherapy compared to treatment as usual at 12 months, in an economic evaluation, using the CSRI to collect health service use, validated using HES/ISD data, and the EQ-5D 5 level (EQ-5D-5L) to calculate Quality Adjusted Life Years (QALYs);
i) 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: General Health V2.0 (WPAI:GH);
j) The treatment fidelity of the manualised Specialist Physiotherapy intervention measured by (i) participant report using a structured telephone survey; (ii) physiotherapist report using a treatment checklist; and (iii) assessment of a random sample of intervention workbooks, which completed during treatment.;
k) The participant's satisfaction with their allocated treatment condition, as measured by a feedback survey;
l) 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;

m) 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.

4 Trial 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. 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.

4.1 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 (Nielsen *et al.*, 2017). The initially planned sample size, which allowed for an anticipated 20% dropout rate, was 264 (132 in each arm). This figure was recently reviewed and it is seen now as a minimum sample size, while a more ambitious sample size of 300 is the new target. The update was necessary to reflect a more conservative estimate of retention based on retention rates at 6 months' post randomisation, now allowing for 30% dropout rate. Following the interruption for COVID-19, an extension was agreed by the funders in April 2021 to recruit another 90 to 120 participants whose treatment will not have been affected by COVID-19.

4.2 Randomisation

Randomisation occurred at the level of the participant, stratified by site. Participants have been randomised with a 1:1 ratio to a novel specialist physiotherapy treatment protocol and TAU groups. Block randomisation with random block sizes has been used to ensure even allocation of intervention and control participants within sites. A detailed Randomization Protocol (v1.1, 29/06/2018) gives further information about how patients are randomized and randomization list is created, stored and used.

5 Data collection

Demographic and clinical baseline data are obtained from both the medical notes and from the participant. Demographic data includes date of birth, gender and ethnicity among others. Clinical data includes symptom phenomenology, symptom duration, past medical history, previous treatments and others.

5.1 Primary outcome measures

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

5.2 Secondary outcome measures

a) Short Form 36 subscales (not PF) and summary scores;
b) Functional Mobility Scale;
c) Objective measures of Health Service Use;
d) Revised Illness Perception Questionnaire;
e) Hospital Anxiety & Depression Scale;
f) Clinical Global Impression Scale of Improvement, 5-point scale (CGI-I);
g) EQ-5D-5L;
h) Client Service Receipt Inventory;
i) Work Productivity & Activity Impairment Questionnaire (WPAI)
j) Fatigue State (single question 5-point scale based on EQ-5D-5L);
k) Extended Patient Health Questionnaire-15 (extended PHQ-15);
l) Confidence in correctness of diagnosis of FMD (10-point scale).

Further details on the outcomes, including a list of references, can be seen in the protocol.

5.3 Assessment of Intervention Fidelity & Satisfaction

In addition to the clinical assessments, the provision of physiotherapy in both groups is monitored with a structured feedback telephone survey. The survey explores the content, number and length of physiotherapy sessions. Intervention adherence will be defined as the participant acknowledging

- Being given the intervention workbook
- Receiving education about their movement problem
- Having discussed how self-focused attention affects FMD
- Having completed a self-management plan
- If they experienced persistent pain at the time of treatment, this was discussed
- If they experienced fatigue at the time of treatment, this was discussed
- If they experienced concentration problems at the time of treatment, this was discussed

The control group will complete the same telephone survey as the intervention group, capturing the number of physiotherapy sessions received and the contents of their treatment. We will also use this data to look for evidence of potential contamination between intervention and control groups. Contamination will be determined by control participants reporting receipt of an intervention workbook (or similar printed material); treatment intensity similar to the intervention group; education about self-focused attention; education/management of persistent pain, fatigue and/or concentration; and completion of a self-management plan.

Satisfaction with allocated treatment will be assessed in both groups with a survey, completed as part of the telephone survey described above.

5.4 Duration of the intervention period and frequency of follow up

The trial duration per participant is 12 months. Participants will complete assessments at baseline and at 6 and 12 months after baseline. Table 1 provides a summary of the times at which data are collected.

Table 1 Schedule of Assessment.

Study Procedures		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		✓	✓	✓
	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				✓	

6 Data analysis plan

6.1 General statistical considerations

All statistical tests and confidence intervals will be 2-sided. Significance will be considered at the 5% level and confidence intervals will be at the 95% level.

Analyses for both primary and secondary outcomes will be conducted following an Intention To Treat (ITT) approach.

6.2 Descriptive analyses

Both the covariates and the outcomes will be summarised using descriptive analysis. Categorical variables shall be reported as frequencies and percentages. Reports of continuous variables shall include mean or median and standard deviation or interquartile range (IQR) as appropriate.

Summary measures for the baseline characteristics will be presented both overall and by randomised group. We will compare baseline characteristics visually to assess whether balance has been achieved. No significance testing will be used. Any notable imbalances may lead to additional adjusted analyses. The number of missing observations will be reported.

A CONSORT flow chart will be provided (Schulz, Altman and Moher, 2010). This will include the number of eligible participants, number of participants agreeing to enter the trial, then by intervention arm: the number continuing through the trial, the number withdrawing at each time point, the number lost to follow-up at each time-point and the numbers excluded/analysed.

6.3 Analysis of primary outcome

The primary outcome is the Physical Function domain of the Short Form 36 Questionnaire (SF36-PF).

The primary outcome will be analysed using random effects modelling, using either therapist or individuals as the random effect, for participants in the intervention and TAU group respectively. This model will control for baseline SF36-PF and it will also adjust for the randomization stratification factor, i.e., site, using fixed effects. The model will be:

$$PF12_{ij} = \beta_0 + \beta_1 \cdot T_{ij} + \beta_2 \cdot PF0_{ij} + \beta_3 \cdot SITE_{ij} + T_{ij} \cdot u_i + (1 - T_{ij}) \cdot w_{ij} + T_{ji} \cdot \varepsilon_{ij}^1 + (1 - T_{ij}) \cdot \varepsilon_{ij}^0,$$

where the *i* subscript denotes the *i*th therapist, the *j* subscript denotes the *j*th participant and

- $PF12_{ij}$ = primary outcome at 12 months;
- T_{ij} = Intervention group indicator;
- $PF0_{ij}$ = primary outcome at baseline;
- $SITE_{ij}$ = Study site indicator;
- $u_i \sim N(0, \sigma_u^2)$ = Therapist-level random effect for the intervention arm;
- $w_{ij} \sim N(0, \sigma_w^2)$ = Patient-level random effect for the TAU arm;
- $\varepsilon_{ij}^0 \sim N(0, \sigma_0^2)$ = Normally distributed error term for TAU arm;
- $\varepsilon_{ij}^1 \sim N(0, \sigma_1^2)$ = Normally distributed error term for the intervention arm.

In case of poor model convergence, we will explore the use of a random effect term to adjust for "site" and fit a three-level mixed-effect model.

This will be a complete-case analysis. Presentation of all findings will be in accordance with the latest CONSORT statement.

6.4 Analysis of secondary outcomes

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 variables. Poisson regression models or suitable alternatives (such as Negative Binomial or Zero Inflated models) depending on the distributions of the relevant outcomes will be used to explore the difference between the randomised groups.

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". Fatigue EQ-5D will be treated similarly. These outcomes will be analysed using mixed effects logistic regressions, adjusting for baseline values (when collected, i.e., not for GCI-I scale) and site using fixed effect, if possible. Other clinical secondary outcomes, measured using continuous scales, will be analysed similarly to the primary outcome, using general linear mixed models (GLMMs) and appropriate family and log links to account for the distribution of the data. Treatment fidelity and participant's satisfaction will be summarised, by arm, using appropriate descriptive statistical methods. Categorical variables will be reported using frequencies and percentages, while continuous variable with mean and standard deviations.

All analyses of secondary outcomes should be considered as supportive and hypotheses-generating analyses.

6.5 Sensitivity and supplementary analyses

We will perform sensitivity analyses looking at the effect of missing data, aiming at identifying predictors of missingness and hence add them into the primary outcome regression model.

We will describe the impact of treatment withdrawals summarising with descriptive statistics the primary endpoints in participants who have withdrawn from treatment but have continued in follow up.

Furthermore, a dose-response analysis will be performed. We will fit an alternative version of the primary outcome model adding the interaction term between the number of sessions attended and the randomised group, to evaluate whether those who attended more sessions in the treatment group show better results.

To evaluate the impact on the trial of St George's Hospital, which is a more specialist centre and it is supposed to treat more complex patients, we will fit a modified version of the primary outcome analysis model where the $SITE_{ij}$ independent variable is replaced by a binary indicator for St George hospital ($STGH_{ij}$).

Participants who have been offered and could participate to at least 5 sessions for either group are considered to be compliers. We will conduct a Complier Average Causal Effect (CACE) sensitivity analysis.

All the above sensitivity analyses will be conducted for the primary outcome only.

Sensitivity analyses to evaluate Covid-19 impact on the study

Descriptive statistics of baseline characteristics for 4 groups of patients will be tabulated. The groups have been identified according to the way the coronavirus pandemic has affected the study and the participant and are as follows:

A. Participants who were able to adhere to the study protocol and completed 12 month follow up by 23 March 2020, i.e., the date when national lockdown restrictions were imposed in the UK (N=23);
B. Participants who were recruited and started treatment before 23 March 2020, but could not complete their 12-months follow up before lockdown came into place and were partially followed up during the pandemic (N=129);

C. Participants who were recruited before 23 March 2020, but who could not start the treatment before then due to the start of the pandemic (N=89);
D. Participants who were recruited in 2021/ 2022 as part of the extension (N=90 to 120).

In a sensitivity analysis, the primary outcome analysis will be fitted only using data from participants belonging to groups A and B (N=170). A similar sub-group sensitivity analysis will be performed using only data from participants in group D (N=90 to 120).

To account for the impact of possible delays in treatment administration due to suspension of non-essential hospital activities in relation to COVID-19 outbreak, a further sensitivity analysis we will be conducted. We will repeat the primary outcome analysis, adding a supplementary fixed effect to the model and its interaction with the assigned treatment, which will thus become

$$PF12_{ij} = \beta_0 + \beta_1 \cdot T_{ij} + \beta_2 \cdot PF0_{ij} + \beta_3 \cdot SITE_{ij} + \beta_4 \cdot COV_{ij} + \beta_5 \cdot \left(COV_{ij} \cdot T_{ij}\right) + T_{ij} \cdot u_i + (1 - T_{ij}) \cdot w_{ij} + T_{ji} \cdot \varepsilon_{ij}^1 + \left(1 - T_{ij}\right) \cdot \varepsilon_{ij}^0,$$

where COV_{ij} would be the patient-level indicator of whether insufficient or no treatment has been administered due to the outbreak of the COVID-19 pandemic (groups B and C in the list above).

6.6 Exploratory analyses

Two outcomes will be determined by a self-rating of "improved" or "much improved" on the CGI-I scale or a 10-point increase in SF36-PF score. Two exploratory analyses of prognostic indicators will use random effects logistic regression modelling to determine predictors of a good or bad outcome from baseline demographic and clinical characteristics. Results 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.

6.7 Model checking

The model for the primary outcome analysis assumes that the residuals are normally distributed and homoscedastic. This will be checked using residuals plots. If substantial departures from normality occur, a transformation of the outcome variable will be considered. Hausman specification test will be used to assess whether the random effect model is superior to the fixed effect one.

6.8 Adverse event reporting

Adverse events (AE) and Serious adverse events (SAE) will be summarised (by both number of events and number of participants). These events are defined in section 18 of the protocol.

7 Software

Data will be downloaded from the trial specific online database provided by Sealed Envelope into a format suitable to be read by Stata. All the statistical analysis will be performed using Stata version 16 (or above) and R version 3.5.0 (or above).

8 Health Economics

8.1 Aims

The primary aim of the health economic analysis is to calculate the mean incremental cost per quality-adjusted life-year (QALY) gained using the EQ-5D-5L of specialist physiotherapy compared to treatment as usual (TAU) at 12 months from a health and social care cost perspective.

Secondary aim:

- Calculate the mean incremental cost per QALY gained of specialist physiotherapy compared to TAU at 12 months from a societal perspective

8.2 Outcomes

8.2.1 EQ-5D-5L

Quality of life will be measured using the EQ-5D-5L collected at baseline, 6 and 12 months' post randomisation. The responses to these questions will be converted to utility weights where the maximum possible score for perfect health is 1, health states equivalent to death are anchored at 0, and scores less than 0 are possible, using the UK tariff set published by Devlin *et al.*, (2018).

8.2.2 Client Service Receipt Inventory (CSRI)

Resource use will be collected using a modified version of the CSRI previously developed and tested for use in patients with FMD as part of the feasibility trial. The CSRI asks about community and secondary health care services, out of pocket costs, help received from family and friends, the cost of transport associated with FMD appointments, any equipment and adaptations made due to the illness and medication costs. This will be completed at baseline, 6- and 12-months post randomisation.

8.2.3 Hospital Episode Statistics (HES) & Information Services Division (ISD)

HES/ISD data will be used to validate the results of the CSRI analysis by:

a) checking the reliability of patient reporting
b) applying more specific costs based on reason of attendance
c) investigating the implications for the cost-effectiveness analysis of including HES/ISD data for patients with missing data on the CSRI due to incomplete data on the CSRI or loss to follow-up

8.2.4 Work Productivity & Activity Impairment – General Health (WPAI-GH)

The WPAI-GH will be used to calculate the cost impact of improved engagement with employment due to specialist physiotherapy.

8.3 Cost data

8.3.3 Cost of specialist physiotherapy

DN: we need detail here on what is being collected on physiotherapist time and what activities that includes.

The cost of the physiotherapist delivering the specialist physiotherapy will be calculated by multiplying the time spent delivering the intervention to each participant by the average cost per hour of a hospital based physiotherapist from the PSSRU to calculate the individual level cost per participant. We will report the mean cost and standard deviation in the intervention arm. Means and standard deviations will also be reported by centre.

We will cost study physiotherapists attendance at a 5-day training programme. The cost of training will be a conservative estimate of the cost per participant enrolled in the trial, given that physiotherapists may have more patients than this on their caseload in practice.

8.3.1 Resource Use

Descriptive statistics for the percentage of participants using a type of contact, and mean number of contacts, for each type of health and social care contacts collected by the modified CSRI will be reported at baseline, 6 and 12 months by group. Information on data completeness will also be reported.

8.3.2 Cost of health and social care resource use

The cost of health and social care resource use for the specialist physiotherapy group versus TAU will be calculated, using the modified CSRI. These will be calculated for each participant using the unit costs from the most recent version of the Unit Costs of Health and Social Care published by the Personal Social Services Research Unit (PSSRU) and NHS reference costs. Medication will be costed using the British National Formulary (BNF) and online sources when not available from the BNF.

Mean cost per participant will be reported for specialist physiotherapy versus TAU as total cost per participant and by type of service use. The difference in health and social care costs between the two groups will be reported. Mean incremental costs will be calculated using regression analysis, adjusting by baseline values and centre with therapist as a random effect. Bootstrapping will be used to calculate 95% CIs.

8.3.4 Wider Societal Costs

Societal costs include out-of-pocket costs collected by the modified CSRI and the cost of losses to productivity due to FMD collected as part of the WPAI-GH. Productivity will be costed using the human capital approach. Participant wages will be based on the median wage of reported

professional group from the most recent version of the ONS Annual Survey of Hours and Earnings *(ASHE - ONS*).

Differences in wider costs between specialist physiotherapy and TAU will be reported. Mean incremental costs will be estimated using regression analysis, adjusting by baseline values, centre and therapist. 95% CIs will be calculated using a bootstrap regression.

8.4 Quality-adjusted life-years

QALYs will be calculated using the area under the curve method using utility values calculated from responses to the EQ-5D-5L collected at baseline, 6 and 12 months, using the formula by Devlin et al., (2017). Mean utility values for each time point and mean unadjusted QALYs from baseline to 12 months will be reported for specialist physiotherapy and TAU. The incremental mean difference in QALYs adjusting for baseline and centre with therapist as a random effect using regression analysis will be reported for both specialist physiotherapy and TAU. Bootstrapping will be used to calculate 95% CIs.

QALYs will also be calculated from the SF-6D and using the algorithm from Brazier and Roberts (2004).

8.5 Discounting

As the analysis is for 12 months no discounting will be included.

8.6 Primary Analysis

8.5.1 Incremental cost-effectiveness ratio (ICER)

We will report mean incremental cost per QALY gained between specialist physiotherapy and TAU at 12 months. Costs will be bootstrap adjusted as specified in section 8.3.2 and will include the cost of health and social care resource use and the cost of specialist physiotherapy.

8.5.2 Cost effectiveness acceptability curve (CEAC) and Cost effectiveness plane (CEP)

The bootstrapped means and 95% CIs for costs and QALYs will be used to calculate the probability that specialist physiotherapy is cost-effective compared to TAU for a range of cost-effectiveness threshold values. We will also report a cost-effectiveness plane showing the bootstrapped results.

8.7 Missing data

Data will be analysed according to randomised groups (i.e. according to intention to treat) and using available-case analysis. The number of missing observations for each outcome at each time point will be reported. Patterns of missingness will be explored, predictors of missingness will be assessed, and the suitability of missing data assumptions considered. Depending on the level and pattern of missing information, we will consider performing multiple imputation or other types of imputation as appropriate, in consultation with the statistician where appropriate to ensure that any variables used in both analyses are treated in a coherent manner.

8.8 Sensitivity Analysis

We will test the impact on the results of:

1. Changing assumptions used to calculate the cost of specialist physiotherapy as described in section 8.3.3.
2. Substituting relevant costs in the CSRI with more specific costs using information from HES/ISD data.

8.8.1 Cost effectiveness acceptability curve (CEAC) and Cost effectiveness plane (CEP)

In line with the statistical analysis we will report mean utility at baseline 6- and 12-months, mean QALYs at 12 months and mean health and social care resource use costs at baseline, 6- and 12-months for each of the 4 groups specified in section 4.5.1.

We will report the ICER, CEAC and CEP for specialist physiotherapy versus TAU at 12 months separately using only participants from groups A and B and then using only participants from group D.
In a sensitivity analysis, the primary outcome analysis will be fitted only using data from participants belonging to groups A and B (N=170). A similar sub-group sensitivity analysis will be performed using only data from participants in group D (N=90 to 120).

To evaluate the implications of any dampening of the treatment effect due to reduced access to care, we will include an analysis where a covariate will be included for if the time point data was collected for fell before, during or after lockdown. We will interrogate the impact of lockdown in particular for 1) EQ-5D-5L utilities; 2) routine secondary care appointments; 3) emergency secondary care contacts..

8.9 Secondary Analysis

Cost-effectiveness from a societal perspective

We will report the ICER, CEAC and CEP for specialist physiotherapy versus TAU at 12 months from a societal perspective.

The ICER, CEAC and CEP will also be reported using the SF-6D to calculate QALYs.

9 References

Annual Survey of Hours and Earnings (ASHE) - Office for National Statistics (no date). Available at: https://www.ons.gov.uk/surveys/informationforbusinesses/businesssurveys/annualsurveyofhoursandearningsashe (Accessed: 3 June 2020).

Brazier, J. E. and Roberts, J. (2004) *The Estimation of a Preference-Based Measure of Health from the*, *Care*.

Devlin, N. J. *et al.* (2018) 'Valuing health-related quality of life: An EQ-5D-5L value set for England', *Health Economics (United Kingdom)*, 27(1), pp. 7–22. doi: 10.1002/hec.3564.

Drummond, M. F. *et al.* (2005) *Methods ofr the Economic Evaluation of Health Care Programmes, 3rd edition*. Oxford University Press.

Nielsen, G. *et al.* (2017) 'Randomised feasibility study of physiotherapy for patients with functional motor symptoms', *Journal of Neurology, Neurosurgery & Psychiatry*, 88(6), pp. 484–490. doi: 10.1136/jnnp-2016-314408.

Schulz, K. F., Altman, D. G. and Moher, D. (2010) 'CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials', *BMC Medicine*. BioMed Central, 8(1), p. 18. doi: 10.1186/1741-7015-8-18.