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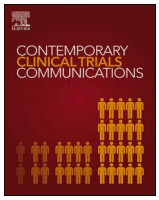

COVID-19 and the Physio4FMD trial: Impact, mitigating strategies and analysis plans

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ABSTRACT

Introduction: Functional motor disorder (FMD) is a common cause of disabling neurological symptoms such as weakness and tremor. Physio4FMD is a pragmatic, multicentre single blind randomised controlled trial to evaluate effectiveness and cost effectiveness of specialist physiotherapy for FMD. Like many other studies this trial was affected by the COVID-19 pandemic.

Methods: The planned statistical and health economics analyses for this trial are described, as well as the sensitivity analyses designed to assess the disruption caused by COVID-19. The trial treatment of at least 89 participants (33%) was disrupted due to the pandemic. To account for this, we have extended the trial to increase the sample size. We have identified four groups based on how participants' involvement in Physio4FMD was affected; A: 25 were unaffected; B: 134 received their trial treatment before the start of the COVID-19 pandemic and were followed up during the pandemic; C: 89 were recruited in early 2020 and had not received any randomised treatment before clinical services closed because of COVID-19; D: 88 participants were recruited after the trial was restarted in July 2021. The primary analysis will involve groups A, B and D. Regression analysis will be used to assess treatment effectiveness. We will conduct descriptive analyses for each of the groups identified and sensitivity regression analyses with participants from all groups, including group C, separately.

Discussion: The COVID-19 mitigation strategy and analysis plans are designed to maintain the integrity of the trial while providing meaningful results.

Trial registration: ISRCTN56136713.

1. Background

Functional motor disorder (FMD) is a common condition seen in neurology and psychiatry services. With an estimated incidence of 4–12 per 100,000 per year, it is at least as common as multiple sclerosis [1]. Patients experience disabling symptoms which may include weakness, tremor, jerks, dystonic postures or an altered gait pattern; alongside non-motor symptoms such as sensory disturbance, cognitive fog, pain, fatigue or functional seizures [2]. Physical rehabilitation based on a biopsychosocial understanding of FMD has emerged as a promising

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treatment. There have been two randomised controlled trials (RCTs), each describing positive outcomes [3,4], but there is an absence of evidence from large adequately-powered multicentre RCTs. The Physio4FMD trial seeks to determine the clinical and cost effectiveness of a specialist physiotherapy intervention compared to treatment as usual (TAU) one year after randomisation for people with FMD, in a pragmatic multicentre RCT [5]. The trial recruitment period was scheduled for September 2018–April 2020, but was interrupted by the COVID-19 pandemic.

The COVID-19 pandemic disrupted most ongoing clinical trials with devastating effects on the conduct of these studies [6–8]. Most were put on hold while clinical expertise was diverted to the pandemic response and non-essential face-to-face appointments were suspended to prevent transmission of the virus. Non-essential NHS appointments and treatments were suspended as part of the initial pandemic response. The Physio4FMD trial was running at 11 sites in England and Scotland when recruitment and trial treatment was suspended in March 2020.

The aims of this paper are to describe the impact of the COVID-19 pandemic on the Physio4FMD trial; to describe the impact-mitigation plan; and to avoid data-driven analysis by describing in detail our statistical and health economics analysis plan ahead of database lock, analysis and unblinding.

2. Impact of COVID-19 on Physio4FMD trial

The trial had a recruitment target range of 264–300. The lower range of this target had already been reached (n = 267) at the time that national COVID-19 lockdown restrictions in the UK commenced on 23 March 2020 and in-person research activity was suspended. The end of the scheduled recruitment period coincided with the height of the first wave of the pandemic in the UK in April 2020. The pandemic response had little impact on follow up data collection. It had always been planned to collect the six and 12-month outcome measures for the trial remotely (via telephone, mail or online form), and data collection continued unimpeded during lockdown restrictions as per protocol.

The main impact of COVID-19 on the trial was the interruption to the delivery of the intervention and control treatments (outpatient physiotherapy). Suspension of non-essential physiotherapy treatment had occurred at all trial sites by mid-March 2020. At this time, 89 participants (33% of the total recruited) had been randomised but were awaiting their allocated treatment. The suspension was then lifted at different times for the trial sites, based on regional variations to the pandemic response. Most sites were given permission to resume physiotherapy treatment with precautions after six to nine months but some sites did not reopen. When physiotherapy treatment restarted, trial participants from both randomised groups were subjected to additional delays in receiving treatment due to the impact of the pandemic on NHS waiting times. As a result, this group of participants did not receive their allocated treatment within their trial follow up period (at least 51 of the 89) or their treatment was substantially delayed. Including these participants in the final analysis as part of an intention to treat (ITT) analysis plan is likely to dilute a potential treatment effect and may result in a type 2 error (a negative trial despite an effective treatment). Other consequences of the pandemic response on the trial are reported later in this paper.

3. Mitigating the impact of COVID-19

Guidance for minimising the impact of COVID-19 on clinical trials has been produced by a number of organisations, including the Medicines and Healthcare products Regulatory Agency [9], European Medicines Agency [10] and Food and Drug Administration [11]. The main message is to evaluate the changes that have been necessary as a result of COVID-19 and develop a plan to mitigate them. In terms of statistical analysis, this is interpreted as collecting as much data as possible, prioritising the more important outcomes, logging protocol deviations as appropriate and planning prior to the database lock to undertake additional analyses to explore the effects of the COVID-19 interruption on trial outcomes.

Recommendations about what to do with follow up data collected from participants who did not receive their trial allocated treatment due to the pandemic have been based on the ICH E9(R1) addendum and the role of intercurrent events [12,13]. The first step is to determine the estimand (treatment effect) of interest. In the case of COVID-19 the potential estimands of interest are (i) the treatment effect in a hypothetical “pandemic free world”; or (ii) the treatment effect in a “world including a pandemic”. In the case of Physio4FMD, the pandemic-influenced scenario will estimate an average treatment effect when a proportion of the population remain untreated. Although COVID-19 may continue to cause disruption to the delivery of physiotherapy treatment and future pandemics are possible, we argue that the initial COVID-19 pandemic response was unique and outcomes that are heavily influenced by these events will not be generalisable. Therefore, the estimand of interest to Physio4FMD is the treatment effect in the absence of the initial pandemic response.

The Physio4FMD trial management group sought external advice from independent statisticians in developing a COVID-19 mitigation plan. In consultation with the Data Monitoring and Ethics Committee, the Trial Steering Committee, Patient and Public Representatives, and the research funder, the following mitigation plan was agreed.

3.1. Extend the trial and increase the sample size

The funder approved a request to extend the trial to recruit an additional 90–120 participants. The lower limit of 90 will allow additional people to cover for those who did not receive timely treatment due to the pandemic. The upper limit of 120 was to mitigate against further possible disruption due to COVID-19 after restart and was a feasible upper target based on previous recruitment rates.

3.2. The primary analysis

Data from participants who were randomised but did not receive treatment before 23 March 2020 (n = 89) will be treated as missing data for the primary analysis. This group either did not receive any treatment during the trial period (12 months post randomisation) or their treatment was substantially delayed and it occurred close to the primary outcome assessment point. We justify this decision in the discussion section of this paper.

3.3. Complete additional sensitivity analyses

A series of sensitivity analyses will be conducted to determine the impact of COVID-19 on the trial outcome. The main sensitivity analysis will include all randomised participants, irrespective of whether COVID-19 prevented them from receiving treatment.

Below we describe in detail our approach to the analysis of the clinical and health economic data.

4. Trial status

Participant recruitment began on 16 November 2018 and was stopped on 16 March 2020 due to COVID-19 restrictions. The total recruitment was n = 267. Follow up of all participants continued remotely as planned, whether or not they received treatment. An extension to the trial was granted by the funder in April 2021. Recruitment restarted in July 2021 and closed on 31 January 2022. An additional 88 participants were recruited, making the total recruitment n = 355. The trial is now in follow up and the anticipated trial end date is September 2023.

5. Patient and public involvement

Patient and public representatives were involved in the design of the trial. Amongst other decisions, their expertise was particularly important in determining whether the research aims were meaningful and the procedures were acceptable. There are two patient representatives on both the independent Trial Steering Committee and the Trial management group, contributing to ongoing oversight and management. Patient representatives are also integral to the dissemination plans.

6. Ethics

Ethical approval was obtained from the London-Surrey Borders Research Ethics Committee, reference number 18/LO/0486, on 28 March 2018. An amendment to encompass changes due to COVID-19 was approved on 15 July 2021.

7. Trial design

The Physio4FMD trial is a pragmatic, multisite, single-blind, parallel group, randomised controlled trial in adults with FMD. The trial intervention is a specialist physiotherapy protocol and the control is TAU (referral to community physiotherapy). Participants are assessed at baseline, 6 and 12 months (primary outcome).

The primary objective is to evaluate the effectiveness of specialist physiotherapy compared to TAU in reducing disability at 12 months post randomisation, as measured by the Physical Function domain of the Short Form 36 questionnaire (SF36-PF) [5,14]. The secondary trial objectives are to evaluate the effect of specialist physiotherapy compared to TAU on a range of health outcomes and to undertake an economic evaluation to assess the cost-effectiveness of the intervention compared to TAU. The secondary objectives and the corresponding outcome measurement tools are listed in Tables 1 and 2.

The original sample size of 264 (132 in each arm) was calculated using data from the preceding single centre feasibility study [4,5]. Unrelated to the pandemic, in February 2020, this figure was reviewed and a more ambitious recruitment target of 300 was set. Recruitment had reached 267 when the trial was paused due to COVID-19. In July 2021, as part of the COVID-19 mitigation strategy, plans were approved to recruit an additional 90 to 120 participants (for reasons described above). The final target range was between 357 and 387 participants. Participants are randomised with a 1:1 ratio to the intervention and control groups, stratified by site. Block randomisation with random block sizes was used to ensure even allocation of intervention and control participants within sites. The randomisation protocol continued as before the COVID-19 pause.

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 the nature of the intervention under investigation.

Table 1
Health related secondary objectives and corresponding assessment tool.

Secondary Objectives	Outcome Assessment Tool
To determine the effectiveness of specialist physiotherapy compared to TAU at 6 and 12 months post randomisation on:	
1. Mobility	Functional Mobility Scale [15]
2. Health-related quality of life.	The seven Short Form 36 domains other than physical functioning (which is the primary outcome) [14]
3. Understanding and illness beliefs	Revised Illness Perception Questionnaire [16]
4. The participant's perception of change	Clinical Global Impression Scale of Improvement (CGI-I) [17]
5. Self-reported anxiety and depression	Hospital Anxiety and Depression Scale [18]
6. Confidence that their diagnosis of FMD is correct.	Confidence in the correctness of the diagnosis, 10-point scale [19]
7. Objective measures of health service use at 12 months. Health service use for this part of the analysis will be considered a proxy-measure of clinical change that is objective and not patient reported	Hospital Episode Statistics (HES) and Information Services Division (ISD) data (digital data held by NHS England and NHS Scotland containing details of all admissions, outpatient appointments and A&E attendances).
8. Subjective measures of health service use at 12 months.	Client Services Receipt Inventory (CSRI) [20]

Table 2
Objectives and assessment tools for the health economic analysis.

Objective	Assessment Tool(s)
1. Calculate the incremental cost of specialist physiotherapy compared to TAU at 12 months from a health and social care cost perspective	(i) Cost of specialist physiotherapy in the specialist physiotherapy arm (ii) Client Service Receipt Inventory [20]
2. Calculate the incremental Quality Adjusted Life Years (QALYs) of specialist physiotherapy compared to TAU at 12 months	(i) EQ-5D 5 level (EQ-5D-5L) [21] to calculate QALYs (ii) SF-36 and SF-6D [22]
3. Calculate the incremental cost of specialist physiotherapy compared to TAU at 12 months using routine data.	Hospital Episode Statistics (HES) and Information Services Division (ISD) data
4. The effectiveness of specialist physiotherapy compared to TAU in enabling continued employment or facilitating return to work at 12 months post randomisation.	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP) [23]
5. Calculate the incremental cost of specialist physiotherapy compared to TAU at 12 months from a wider cost perspective.	(i) Cost of specialist physiotherapy in the specialist physiotherapy arm (ii) Client Service Receipt Inventory [20] (iii) WPAI:SHP

8. Statistical analysis plan

8.1. General considerations

Four groups have been identified to reflect the manner in which the COVID-19 pandemic impacted the trial. The four groups are as follows.

Group A (n = 25): Participants who received their treatment as described in the protocol and or completed their 12-month follow up by 23 March 2020, that is, the date when national lockdown restrictions were imposed in the UK.
Group B (n = 134): Participants who were recruited and received their treatment as described in the protocol before 23 March 2020, but were still in follow up when lockdown came into place and completed their 12-month follow up after 23 March 2020.
Group C (n = 89): Participants who were recruited and randomised before 23 March 2020, but could not complete their treatment before this date due to the pandemic.
Group D: (n = 88) Participants recruited after July 2021 as part of the trial extension.

Currently, there are n = 19 participants who have withdrawn from follow up or are missing 12 month follow up data. These participants are not represented in Groups A-D above. Recruitment rate by group is displayed in Fig. 1.

The potential impact of the pandemic response for each group is described in Table 3.

All statistical tests and confidence intervals will be two-sided. Statistical significance will be considered at the 5% level and estimates will be presented with 95% confidence intervals. Analyses for the primary outcome and main secondary outcomes will involve only groups A, B and D as discussed below and will follow Intention to Treat (i.e. participants will be analysed in the arm to which they were randomised, irrespective of treatment withdrawal, noncompliance or crossover

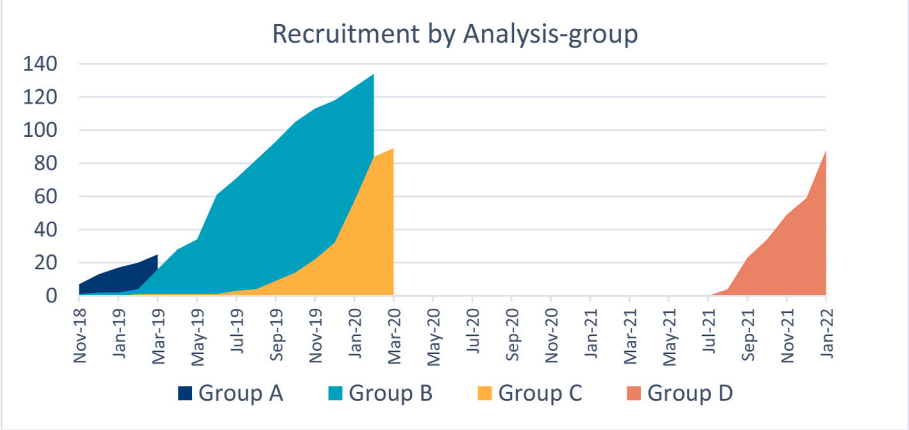

Fig. 1. Recruitment rate by analysis-group.

between trial arms). Group C will take part in a sensitivity analysis only. The analysis of the primary and secondary outcomes will be conducted following a complete-case approach. Presentation of all findings will be in accordance with the latest CONSORT statement [24]. The impact of missing data on the primary outcome will be explored in a supplementary analysis.

8.2. Descriptive statistics

Both the covariates and the outcomes will be summarised using descriptive analysis. Categorical variables will be reported as frequencies and percentages. Reports of continuous variables will include mean or median and standard deviation or interquartile range as appropriate. The number of missing observations will also be reported. Summary measures for the baseline characteristics will be presented overall and by treatment arm. No formal statistical tests will be performed to compare baseline characteristics; hence any observed differences between the treatment arms will be due to chance rather than randomisation bias. A CONSORT flow chart will be provided [24]. This will include the number of participants: agreeing to enter the trial; continuing through the trial by randomised arms; withdrawing at each follow up time point; lost to follow up at each time-point and excluded/analysed. The reasons for exclusion or withdrawal when known will be reported.

8.3. Analysis of primary outcome

The primary outcome analysis will be fitted using data from participants belonging to groups A, B, and D. It will be analysed using random effects modelling [25,26], with either therapist or individuals as the random effect, for all participants in the specialist physiotherapy and TAU group respectively. This model will control for baseline SF36-PF values and it will also adjust for the randomisation stratification factor, that is, site, using fixed effects. The model will be:

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

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.

The model for the primary outcome analysis assumes that the residuals are normally distributed and homoscedastic. These assumptions will be checked using residuals plots. If substantial departures from normality occur, analogous methods which do not have such assumptions will be explored. Hausman specification test [27] will be used to assess whether the random effect model is superior to the fixed effect one. 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 [28].

8.4. Analysis of secondary outcomes

For Hospital Episode Statistics (HES) and Information Services Division (ISD) digital data, we will report descriptive statistics for each type of service (i.e., outpatient, Accident and Emergency (A&E), inpatient). Suitable descriptive statistics and statistical tests will be selected depending on the distribution of the variables. Mixed effects 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 dichotomised into (i) good outcome, and (ii) poor outcome. Good outcome will be defined as ratings of “much improved” or “improved” and poor outcome will be defined as a rating of “same”, “worse”, or “much worse”. The 5-point Fatigue State scale will be dichotomised into (i) extreme and severe fatigue; and (ii) moderate, slight or no fatigue. Analysis for the dichotomised scales will use mixed effects logistic regressions, adjusting for baseline values (when collected, i.e., not for CGI-I scale as it is not collected at baseline because it is a measure of change) and site using fixed effects, if possible. Other clinical secondary outcomes, measured using continuous scales, will be analysed similarly to the primary outcome, using linear mixed models and adjusting for baseline values.

Adverse events (AE), and serious adverse events (SAE) will be summarised, by both number of events and number of participants.

8.5. Sensitivity analysis to evaluate the impact of COVID-19

Descriptive statistics of baseline characteristics for the 4 groups of participants (A – D) will be tabulated by randomised treatment.

To account for the impact of possible delays in starting treatment due

Table 3
Potential impact of the pandemic response by COVID-19 affected groups.

Impact of COVID-19	Description	Mitigating Strategy
Treatment delays (Group C)	Suspension of research and non-essential NHS services led to substantial delays for participants waiting to receive their trial treatment. In many cases, treatment occurred close to the final 12-month post randomisation assessment. The impact of this on outcome is unclear. If there is a loss of treatment effect over time, the reduced follow up period may inflate a treatment effect size. Conversely, delays may have reduced a treatment effect if longer symptom duration and/or living with FMD during lockdown restriction is associated with worse outcomes. It is possible that delays had different effects on the intervention and control groups.	Participants who experienced delayed treatment or no treatment due to the initial pandemic response (Group C) will not be included in the primary analysis. Sensitivity analyses will explore the impact of delays on treatment in the intervention and control groups.
Allocated treatment not received (Group C)	A proportion of participants who had not received their allocated treatment by 23 March 2020, did not receive any treatment during the trial follow up period. This is likely to dilute a potential treatment effect and may lead to a type 2 error (a negative trial, despite an effective intervention).	
Altered patterns of health and social care utilisation impacting on the health economic analysis (Groups B & C)	Suspension of non-essential NHS services and discouragement from attending A&E for non-life-threatening ailments is likely to have caused reduced health and social care utilisation at 6 and 12 month follow ups. Rates of unemployment may have also been affected, as many workers were placed on furlough.	Both the intervention and control groups should be affected equally, however if resource use is close to zero it may not be possible to detect differences.
Influence on how participants answered outcome assessments (Groups B & C)	The outcomes reported by participants who completed follow up during the pandemic may be negatively influenced include the measurement domains of anxiety, depression, social interaction, work/ employment and physical activity.	These more subtle effects of the pandemic may be difficult to detect. A sensitivity analysis comparing groups B&C with A&D may provide some insight, although there may be insufficient numbers to identify patterns in the data.
Potential influence on the primary outcome measure (Groups B & C)	The primary outcome measure (SF36-PF) asks participants if their health limits their ability to complete a range of physical activities ranging from vigorous activity such as participating in sports, to climbing several flights of stairs and walking various distances. We do not expect lockdown restrictions to have had a substantial impact on the primary outcome. However, it is possible that for some participants the pandemic "stay-at-home" orders resulted in reduced levels of physical activity and ultimately lower physical function scores.	

to suspension of non-essential hospital activities in relation to the COVID-19 pandemic, a sensitivity analysis will be conducted and will include all participants (groups A, B, C and D). 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

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

where COV_{ij} is the patient-level indicator of whether insufficient or no treatment has been administered due to the outbreak of the COVID-19 pandemic (i.e. group C).

Further sensitivity analyses to evaluate whether there is indication of a different treatment effect in a post COVID-19 world will be conducted. This will be explored by fitting the model for the primary outcome analysis on two different cohorts, one only using data from groups A and B and the other only from those in group D.

8.6. Other sensitivity and supplementary analyses

The following sensitivity and supplementary analyses are planned for the primary outcome measure only.

1. We will conduct a Complier Average Causal Effect (CACE) sensitivity analysis [29]. Participants who have been offered and could participate in at least five sessions in the intervention group will be deemed as being compliers.
2. To examine the effect of missing data, we will identify predictors of missingness and add them into the primary outcome regression model.
3. We will describe the impact of treatment withdrawals using descriptive statistics to summarise the primary endpoints for participants who have withdrawn from treatment but have continued in follow up.
4. 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 treatment, to evaluate whether the finding in those who attended more sessions in the treatment groups differed.

9. Health economic analysis plan

The Health Economics analysis plan (HEAP) has been written in line with reporting standards to ensure the transparency and reproducibility of economic evaluations [30]. The primary aim of the health economic analysis is to calculate the mean incremental cost per QALY gained (using the EQ-5D-5L) of specialist physiotherapy compared to TAU at 12 months from a health and social care cost perspective. The secondary aim is to calculate the mean incremental cost per QALY gained of specialist physiotherapy compared to TAU at 12 months from a wider cost perspective.

9.1. Outcomes

9.1.1. EQ-5D-5L

A preference-based measure of health-related quality of life, EQ-5D-5L, will be 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, death is anchored at 0, and scores less than 0 are possible using the UK tariff set published by Devlin et al., 2018 [31].

9.1.2. Client service receipt inventory (CSRI)

Resource use will be collected using a modified version of the CSRI [20] previously developed and tested for use in patients with FMD as part of the feasibility trial [4]. The CSRI collects information about community and secondary 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 asking about the previous 6 months.

9.1.3. Hospital episode statistics (HES) & Information Services Division (ISD) data

HES/ISD data will be used to validate the results of the incremental costs calculated from the CSRI by: (i) Checking the reliability of patient reporting; (ii) Applying more specific secondary care costs based on reason for attendance; and (iii) Using HES/ISD data to calculate mean incremental health and social care costs of specialist physiotherapy compared to TAU at 12 months.

9.1.4. Work productivity & activity impairment – specific health problem (WPAI-SHP)

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

9.2. Costs

9.2.1. Cost of specialist physiotherapy

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 hospital-based physiotherapy from the Personal Social Services Research Unit (PSSRU) to calculate the individual level cost per participant. Time spent delivering the intervention will be calculated at 1.5 h per session to account for organisation and administration. Treatment costs will include 30 min of clinical supervision per intervention-participant (as per trial protocol). We will cost intervention-group physiotherapists' attendance at a five-day (37.5 h) training programme and divide by the number of participants in the specialist physiotherapy arm to calculate the cost per participant. The cost of training will be a conservative estimate of the cost per participant given physiotherapists may have more patients than this on their caseload in practice.

9.2.2. Cost of treatment as usual

Participants randomised to the TAU arm are asked to report physiotherapy appointments received as part of the trial in a telephone interview [5]. Physiotherapy appointments will be costed based on the unit cost for a community physiotherapy appointment [32], with an uplift for average travel time for home appointments.

9.2.3. 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 resource use reported in the modified CSRI [20]. 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 PSSRU [32] and NHS Schedule of Reference Costs [33]. Medication will be costed using the British National Formulary (BNF) and online sources when not available from the BNF [34]. NHS Schedule of Reference Costs [33] will also be applied to HES/ISD data as part of the secondary analysis using this data.

9.2.4. Wider societal costs

Wider societal costs include out-of-pocket costs and impact on carer time collected by the modified CSRI and the cost of losses to productivity due to FMD collected as part of the WPAI-SHP. 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 Office for National Statistics Annual Survey of Hours and Earnings [35]. Carer time will be costed as the unit cost per hour for a social care worker [32].

9.3. Quality adjusted life-years (QALYs)

QALYs will be calculated using the area under the curve method [36] using utility values calculated from responses to the EQ-5D-5L collected at baseline, 6 and 12 months, and the EQ-5D-5L valuation study by Devlin et al. [31]. The cross-walk algorithm with the EQ-5D 3 level (EQ-5D-3L) by van Hout et al. [37] will be included as a sensitivity analysis. QALYs will also be calculated using the Short-Form Six Dimension health index (SF-6D), using the algorithm from Brazier et al. [22] applied to SF36 data.

9.4. Discounting

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

9.5. Analysis

In line with the statistical analysis, the primary health economic analysis will exclude participants whose treatment was affected by COVID-19 (Group C).

9.5.1. Descriptive statistics

Descriptive statistics for the percentage of participants using a type of contact, and mean number of contacts for those with non-zero 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.

We will report the mean cost per participant and standard deviation for the cost of specialist physiotherapy and referral to community physiotherapy (excluding private physiotherapy).

Mean cost per participant will be reported for specialist physiotherapy versus TAU as total cost per participant and type of service use. The difference in health and social care costs and wider societal costs between the two groups 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% Confidence Intervals.

Mean utility per participant 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 between specialist physiotherapy and TAU adjusting for baseline and centre with therapist as a random effect using regression analysis will be reported [36] for both specialist physiotherapy and TAU. Bootstrapping will be used to calculate 95% CIs.

9.5.2. Incremental cost-effectiveness ratio (ICER)

We will report mean incremental cost per QALY gained between specialist physiotherapy and TAU at 12 months adjusting for baseline and centre with therapist as a random effect. Costs will be as specified above and will include the cost of health and social care resource use and the cost of specialist physiotherapy. 95% CIs will be calculated using two-part bootstrapping.

9.5.3. 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 [38].

9.5.4. Missing data

Data will be analysed using a complete-case analysis, excluding group C in line with the statistical 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 as appropriate, in consultation with the statistician, to ensure that any assumptions are consistent across analyses.

9.5.5. Validating HES/ISD data

We will report the level of agreement between CSRI and HES/ISD data on matching variables (inpatient, outpatient and A&E attendances). Agreement will be tested using the paired t-tests for normally distributed variables and the Wilcoxon Signed Rank Test for skewed variables.

9.5.6. Sensitivity analysis to evaluate the impact of COVID-19 on cost-effectiveness results

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 four levels of COVID-19-affected groups. We will report the ICER, CEAC and CEP for specialist physiotherapy versus TAU at 12 months separately using participants who were treated before the pandemic (groups A & B) and then using only participants from group D to evaluate the cost-effectiveness of receiving treatment after service availability has been impacted by COVID-19.

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 the time point data was collected (before, during or after lockdown). We will explore the impact of lockdowns in particular for (i) EQ-5D-5L utilities; (ii) routine secondary care appointments; and (iii) emergency secondary care contacts.

9.5.7. Other sensitivity analyses

To explore the uncertainty around costs used in our analysis we will test the impact of changing assumptions used to calculate the cost of specialist and community physiotherapy.

9.5.8. Secondary analysis

1. We will report the ICER, CEAC and CEP for specialist physiotherapy versus TAU at 12 months from a wider cost perspective.
2. We will report the ICER, CEAC and CEP for specialist physiotherapy versus TAU at 12 months using HES/ISD data to calculate costs.
3. The Devlin et al. [31] value set for England has been chosen as our primary analysis of cost-effectiveness given that it has been shown to be more responsive to changes in anxiety and depression [39]. NICE recommends the use the EQ-5D-3L mapping algorithm by van Hout et al. [37] for technology assessment submissions. As a result, we will conduct a secondary analysis using the EQ-5D-3L mapping algorithm.
4. The ICER, CEAC and CEP comparing specialist physiotherapy to TAU from a health and social care cost perspective will also be reported using the SF-6D to calculate QALYs.

10. Discussion

In this paper we have described the impact of the COVID-19 pandemic on the Physio4FMD trial; outlined the impact-mitigating strategies initiated; and detailed the planned statistical and health economic analysis to avoid outcome reporting bias and data-driven analyses.

The interruption of the study due to COVID-19 together with the type of treatments under evaluation raised a unique set of problems. Even though the minimum recruitment target was achieved, due to waiting times to start treatment coupled with a surge in recruitment prior to the pandemic lockdown, a substantial number of participants (33%) did not receive their randomly allocated treatment as described in the protocol. Some participants did receive their treatment after delays of 6 months or more, but many did not receive any treatment during the 12 months trial follow up period. The trial did not have difficulty collecting 6 and 12-month outcome data over the COVID-19 lockdowns as follow ups were done remotely. This means that that missing data will be minimal.

The decisions regarding how to mitigate the impact of COVID-19 was given substantial consideration. We sought external advice from an expert group of statisticians, the Data Monitoring and Ethics Committee, the Trial Steering Committee, the funder (NIHR) and patient and public representatives to ensure that with our plans we produced meaningful results while maintaining the integrity of the trial. The need to augment the sample size with additional participants was clear. However, how to handle the data from the trial participants affected by the fall out of the pandemic was less obvious. An important point for consideration was the interpretation of the principles of ITT analysis. We initially considered the conservative approach, that is, including all randomised participants in the primary analysis, regardless of whether COVID-19 prevented them from receiving timely treatment or not. In this scenario, the effect of being randomised to the intervention group would be diluted. The variance in the data is likely to increase and the probability of showing a difference between randomised groups will be diminished. The study would most likely be under powered and the trial results, regardless of statistical significance, would not be meaningful.

In light of this and in line with recommendations from Cro et al., 2020 [13] we have opted to consider data from the 89 participants whose timely treatment was prevented by COVID-19 as missing data with respect to the estimand of interest for the primary analysis. All other participants will be analysed in the primary analysis according to ITT principles. ITT principles are designed to minimise bias and over-estimates of treatment efficacy due to withdrawal, noncompliance and group crossover [40]. ITT was not designed to deal with the consequences of the interruption of research due to unexpected rare events such as a global pandemic. By excluding the COVID-19 affected participants from the primary analysis, we will preserve the statistical power of the trial. We feel that this approach would yield a more meaningful and generalisable result without diluting the treatment effect size. Thus, in the event of a negative trial, the lack of treatment effect cannot be blamed on the initial pandemic response. We have outlined the planned sensitivity analyses, which both explore the impact of including participants whose treatment was affected by COVID-19 and analyse sub-cohorts of interest separately. The main scope of all the sensitivity analyses would be to determine whether the estimated treatment effects from the regression models are analogous to those of the primary analysis in terms of direction and magnitude.

In line with Meyer et al. [41], we completed a risk assessment on the trial and were able to group participants by the effect COVID-19 had on their trial journey. This enabled us to see the extent of the effect of the COVID-19 interruption and to work out the natural groupings that we could justifiably analyse together for sensitivity purposes. Clearly the unaffected group (A) would be the ideal group to analyse on their own as these participants are unaffected by COVID-19. Unfortunately, any meaningful analyses on this group, apart from producing descriptive statistics, would be limited because of the small number of participants.

Most participants completed their follow up assessments after COVID-19 restrictions had been initiated. Although we suspect the effect will not be great, the pandemic may have had an impact on how participants completed the primary outcome measure (SF36-PF). The SF36-PF asks participants if their health limits their ability to complete a range of physical activities ranging from participating in sports, climbing several flights of stairs and walking various distances, to less vigorous activities such as bathing and dressing. It is conceivable that the lockdown "stay at home" orders and advice for the clinically vulnerable to self-isolate may have reduced levels of physical activity and artificially lowered scores of physical functioning. Likewise, the secondary outcome measures may also be affected, for example, participants may report higher (or indeed lower) levels of anxiety and depression.

The cost-effectiveness analyses are likely to be affected by the delays in treatment, the impact of lockdown on healthcare resource use [42], and changes to health-related quality of life [43]. It is reasonable to assume that access to healthcare resources will have been affected in the same way for both groups; however, if resource use was close to zero regardless of the pandemic, we may not be able to detect an effect. By adjusting for site, we will be able to account for some of the differences in access to healthcare across different parts of the country due to regional differences in COVID-19 case levels over the course of the pandemic [44]. Similarly, whilst participants in both groups may have been affected by the pandemic equally, the full potential benefits of specialist physiotherapy may not be captured by the results of the EQ-5D-5L due to the impact of the pandemic. For example, health-related changes in usual activities on the ED-5D-5L may not have been captured effectively due to the disruption in usual activities during lockdowns. Responses to the anxiety and depression domains may reflect individuals' perceptions and experience of the pandemic [45], with any benefits of the intervention being reduced as a result.

In summary, the COVID-19 pandemic caused a substantial disruption to the Physio4FMD trial by preventing timely treatment for 33% of participants who were recruited prior to March 2020. Other effects of the pandemic on the trial results may come to light once the database is locked and the data analysed. Here we have reported how we have accommodated for the effects of the pandemic and our analysis plans. Some of these ideas could be applied to other similar trials having encountered the same dilemmas due to the pandemic.

Ethics

Ethical approval was obtained from the London-Surrey Borders Research Ethics Committee, reference number 18/LO/0486, on 28 March 2018. An amendment to encompass changes due to COVID-19 was approved on 15 July 2021.

Authors' contributions

GN, LM, IN, AC, ME, LHG, JM, MR, JS, RMH: Conceptualization; GN, LM, IN, AC, ME, LHG, JM, MR, JS, RMH: Funding acquisition; GN, LM, IN, AC, ME, LHG, JM, MR, JS, RMH: Roles/Writing - original draft: FR, LM, MLN, RH, IN and GN; Writing - review & editing: All authors contributed to subsequent drafts and approved the final manuscript.

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Declaration of competing interest

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None of the other authors have competing interests to declare.

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List of Abbreviations

A&E	Accident and Emergency
AE	Adverse Event
BNF	British National Formulary
CACE	Complier Average Causal Effect
CEAC	Cost-Effectiveness Acceptability Curve
CEP	Cost-Effectiveness Plane
CGI-I	Clinical Global Impression Scale of Improvement
CSRI	Client Services Receipt Inventory
EQ-5D-5L	EuroQuol, 5 Dimensions, 5 Levels
FMD	Functional Motor Disorder
HES	Hospital Episode Statistics
ICER	Incremental Cost-Effectiveness Ratio
ISD	Information Services Division
ITT	Intention to Treat
NIHR	National Institute for Health and Care Research
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life-Years
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SF-6D	Short Form Six Dimension
SF36-PF	Short Form 36, Physical Function domain
TAU	Treatment As Usual

WPAI:SHP Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0

References

[1] A. Carson, A. Lehn, Epidemiology, in: M. Hallett, J. Stone, A. Carson (Eds.), Functional Neurologic Disorders, Vol 139 of the Handbook of Clinical Neurology Series, Elsevier, Amsterdam, 2016, pp. 47–60.

[2] A.J. Espay, S. Aybek, A. Carson, M.J. Edwards, L.H. Goldstein, M. Hallett, et al., Current concepts in diagnosis and treatment of functional neurological disorders, JAMA Neurol. 75 (2018) 1132–1141.

[3] A.A. Jordbru, L.M. Smedstad, O. Klungsøyr, E.W. Martinsen, Psychogenic gait disorder: a randomized controlled trial of physical rehabilitation with one-year follow-up, J. Rehabil. Med. 46 (2014) 181–187.

[4] G. Nielsen, M. Buszewicz, F. Stevenson, R. Hunter, K. Holt, M. Dudziec, et al., Randomised feasibility study of physiotherapy for patients with functional motor symptoms, J. Neurol. Neurosurg. Psychiatry 88 (2017) 484–490.

[5] G. Nielsen, J. Stone, M. Buszewicz, A. Carson, L.H. Goldstein, K. Holt, et al., Physio4FMD: protocol for a multicentre randomised controlled trial of specialist physiotherapy for functional motor disorder, BMC Neurol. 19 (2019).

[6] E.J. Mitchell, K. Ahmed, S. Breeman, S. Cotton, L. Constable, G. Ferry, et al., It is unprecedented: trial management during the COVID-19 pandemic and beyond, Trials 21 (2020) 1–7.

[7] J. Thornton, Clinical trials suspended in UK to prioritise covid-19 studies and free up staff, BMJ 368 (2020) m1172.

[8] A. van Dorn, COVID-19 and readjusting clinical trials, Lancet 396 (2020) 523–524.

[9] MHRA, Guidance on Minimising Disruptions to the Conduct and Integrity of Clinical Trials of Medicines during COVID-19, 2020. https://www.gov.uk/guidance/guidance-on-minimising-disruptions-to-the-conduct-and-integrity-of-clinical-trials-of-medicines-during-covid-19. (Accessed 5 January 2022).

[10] EMA, Points to Consider on Implications of Coronavirus Disease (COVID-19) on Methodological Aspects of Ongoing Clinical Trials, 2020. https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical_en-0.pdf. (Accessed 5 January 2022).

[11] FDA, Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency Guidance for Industry, Investigators, and Institutional Review Boards for Questions on Clinical Trial Conduct during the COVID-19 Pandemic, Please Email Clinicaltri, 2020.

[12] EMA. ICH, E9 (R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials - Step 2b, 2017.

[13] S. Cro, T.P. Morris, B.C. Kahan, V.R. Cornelius, J.R. Carpenter, A four-step strategy for handling missing outcome data in randomised trials affected by a pandemic, BMC Med. Res. Methodol. 20 (2020) 1–12.

[14] H.E. Syddall, H.J. Martin, R.H. Harwood, C. Cooper, A. Aihie Sayer, The SF-36: a simple, effective measure of mobility-disability for epidemiological studies, J. Nutr. Health Aging 13 (2009) 57–62.

[15] H.K. Graham, A. Harvey, J. Rodda, G.R. Nattrass, M. Pirpiris, The functional mobility scale (FMS), J. Pediatr. Orthop. 24 (2004) 514–520.

[16] R. Moss-Morris, J. Weinman, K.J. Petrie, R. Horne, L.D. Cameron, D. Buick, The revised illness perception questionnaire (IPQ-R), Psychol. Health 16 (2002) 1–16.

[17] M. Sharpe, J. Walker, C. Williams, J. Stone, J. Cavanagh, G. Murray, et al., Guided self-help for functional (psychogenic) symptoms: a randomized controlled efficacy trial, Neurology 77 (2011) 564–572.

[18] A.S. Zigmond, R.P. Snaith, The hospital anxiety and depression scale, Acta Psychiatr. Scand. 67 (1983) 361–370.

[19] L.H. Goldstein, J.D.C. Mellers, S. Landau, J. Stone, A. Carson, N. Medford, et al., COgnitive behavioural therapy vs standardised medical care for adults with Dissociative non-Epileptic Seizures (CODES): a multicentre randomised controlled trial protocol, BMC Neurol. 15 (2015) 98.

[20] J. Beecham, M. Knapp, Costing psychiatric interventions, Discussion Paper 1536, https://www.pssru.ac.uk/pub/dp1536.pdf, 1999. Accessed 5 Jan 2022.

[21] M. Herdman, C. Gudex, A. Lloyd, M. Janssen, P. Kind, D. Parkin, et al., Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L), Qual. Life Res. 20 (2011) 1727–1736.

[22] J. Brazier, J. Roberts, M. Deverill, The estimation of a preference-based measure of health from the SF-36, J. Health Econ. 21 (2002) 271–292.

[23] J. Lenneman, S. Schwartz, D.L. Giuseffi, C. Wang, Productivity and health: an application of three perspectives to measuring productivity, J. Occup. Environ. Med./American College of Occupational and Environmental Medicine 53 (2011) 55–61.

[24] K.F. Schulz, D.G. Altman, D. Moher, CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials, BMC Med. 8 (2010) 18.

[25] C. Roberts, S.A. Roberts, Design and analysis of clinical trials with clustering effects due to treatment, Clin. Trials 2 (2005) 152–162.

[26] S.W. Raudenbush, A.S. Bryk, Hierarchical Linear Models: Applications and Data Analysis Methods, Second, Sage Publications, 2002.

[27] J.A. Hausman, Specification tests in econometrics, Applied Econometrics 46 (1978) 1251–1271.

[28] S. Rabe-Hesketh, A. Skrondal, Volume I: Continuous Responses, Multilevel and Longitudinal Modeling Using Stata, Stata Press, Texas, 2022.

[29] R.J. Little, L.H.Y. Yau, Statistical techniques for analyzing data from prevention trials: treatment of No-shows using rubin's causal model, Psychol. Methods 3 (1998) 147–159.

[30] J.C. Thorn, C.F. Davies, S.T. Brookes, S.M. Noble, M. Dritsaki, E. Gray, et al., Content of health economics analysis plans (HEAPs) for trial-based economic evaluations: expert delphi consensus Survey, Value Health 24 (2021) 539–547.

[31] N.J. Devlin, K.K. Shah, Y. Feng, B. Mulhern, B. van Hout, Valuing health-related quality of life: an EQ-5D-5L value set for England, Health Econ. 27 (2018) 7–22.

[32] L.A. Curtis, A. Burns, Unit Costs of Health & Social Care 2020, Unit Costs of Health and Social Care, PSSRU, University of Kent. Kent Academic Repository, 2020, https://doi.org/10.22024/UniKent/01.02.84818.

[33] NHS England, National Cost Collection for the NHS, 2020. https://www.england.nhs.uk/national-cost-collection/. (Accessed 5 January 2022).

[34] Joint Formulary Committee, British National Formulary (Online) London, BMJ Group and Pharmaceutical Press, 2020.

[35] Office of National Statistics (ONS), Annual Survey of Hours and Earnings (ASHE) - Office for National Statistics, 2020. https://www.ons.gov.uk/surveys/informationforbusinesses/businesssurveys/annualsurveyofhoursandearningsashe. (Accessed 5 January 2022).

[36] R.M. Hunter, G. Baio, T. Butt, S. Morris, J. Round, N. Freemantle, An educational review of the statistical issues in analysing utility data for cost-utility analysis, Pharmacoeconomics 33 (2015) 355–366.

[37] B. Van Hout, M.F. Janssen, Y.S. Feng, T. Kohlmann, J. Busschbach, D. Golicki, et al., Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets, Value Health 15 (2012) 708–715.

[38] E. Fenwick, K. Claxton, M. Sculpher, Representing uncertainty: the role of cost-effectiveness acceptability curves, Health Econ. 10 (2001) 779–787.

[39] M. Franklin, A. Enrique, J. Palacios, D. Richards, Psychometric assessment of EQ-5D-5L and ReQoL measures in patients with anxiety and depression: construct validity and responsiveness, Qual. Life Res. 30 (2021) 2633–2647.

[40] S.K. Gupta, Intention-to-treat concept: a review, Perspect Clin Res 2 (2011) 109.

[41] R. Daniel Meyer, B. Ratitch, M. Wolbers, O. Marchenko, H. Quan, D. Li, et al., Statistical issues and recommendations for clinical trials conducted during the COVID-19 pandemic, Stat. Biopharm. Res. 12 (2020) 399–411.

[42] C. Propper, G. Stoye, B. Zaranko, The wider impacts of the coronavirus pandemic on the NHS, Fisc. Stud. 41 (2020) 345–356.

[43] D. Long, J.A. Haagsma, M.F. Janssen, J.N. Yfantopoulos, E.I. Lubetkin, G.J. Bonsel, Health-related quality of life and mental well-being of healthy and diseased persons in 8 countries: does stringency of government response against early COVID-19 matter? SSM Popul Health 15 (2021).

[44] L.E. Smith, H.W.W. Potts, R. Amlôt, N.T. Fear, S. Michie, G.J. Rubin, Tiered restrictions for COVID-19 in England: knowledge, motivation and self-reported behaviour, Publ. Health 204 (2022) 33–39.

[45] R.G. White, C. van der Boor, Impact of the COVID-19 pandemic and initial period of lockdown on the mental health and well-being of adults in the UK, BJPsych Open 6 (2020).