


# BMJ Open Randomised, controlled, open-label pragmatic trial evaluating changes in functional exercise capacity after primary care *P*ulmonary *R*Ehabilitation in patients with long COVID: protocol of the PuRe-COVID trial in Belgium

Tess Volckaerts <sup>1,2</sup>, Dirk Vissers,<sup>1</sup> Chris Burtin,<sup>3</sup> Xavier Van Meerbeeck,<sup>4</sup> Kevin de Soomer,<sup>4</sup> Ellie Oostveen,<sup>4</sup> Kim Claes,<sup>2</sup> Ella Roelant,<sup>2</sup> Iris Verhaegen,<sup>2</sup> Michiel Thomeer,<sup>5,6</sup> Maarten Criel,<sup>5</sup> Kirsten Quadflieg,<sup>3</sup> Dries Cops,<sup>3</sup> David Ruttens,<sup>5,6</sup> Thérèse S Lapperre<sup>4,7</sup>

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For numbered affiliations see end of article.

## Correspondence to

Tess Volckaerts;  
tess.volckaerts@uza.be

## ABSTRACT

**Introduction** Long COVID is a prevalent condition with many multisystemic symptoms, such as fatigue, dyspnoea, muscle weakness, anxiety, depression and sleep difficulties, impacting daily life and (social and physical) functioning. Pulmonary rehabilitation (PR) may improve physical status and symptoms of patients with long COVID, yet the evidence is limited. Therefore, this trial aims to study the effect of primary care PR on exercise capacity, symptoms, physical activity and sleep in patients with long COVID.

**Methods and analysis** PuRe-COVID is a prospective, pragmatic, open-label, randomised controlled trial. A sample of 134 adult patients with long COVID will be randomised to a 12 week PR programme in primary care, supervised by a physiotherapist or to a control group, following no PR. A 3 month and 6 month follow-up period is foreseen. The primary endpoint will be the change in exercise capacity measured by 6-minute walk distance (6MWD) at 12 weeks, hypothesising a more significant improvement in the PR group. Other parameters, such as pulmonary function tests (including maximal inspiratory pressure/maximal expiratory pressure), patient-reported outcomes (COPD Assessment Test, modified Medical Research Council Dyspnoea Scale, Checklist Individual Strength, post-COVID-19 Functional Status, Nijmegen questionnaire, Hospital Anxiety and Depression Scale, Work Productivity and Activity Impairment Questionnaire and EuroQoL-5D-5L), physical activity measured by an activity tracker, hand grip strength and sleep efficiency, are secondary and exploratory outcomes.

The recruitment started on 19 April 2022, and 52 patients were included as of 14 December 2022.

**Ethics and dissemination** Ethical approval was obtained in Belgium from the relevant institutional review boards on 21 February 2022 (Antwerp University Hospital, approval number 2022-3067) and on 1 April 2022 (Ziekenhuis Oost-Limburg in Genk, approval number Z-2022-01). Findings from this randomised controlled trial will be disseminated

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This randomised controlled trial in patients with long COVID studies the effect of primary care pulmonary rehabilitation (PR) as compared with controls without PR to account for the natural recovery of long COVID.
- ⇒ A 5-phases primary care rehabilitation programme intervention is studied, taking potential postexertional malaise into account.
- ⇒ A comprehensive assessment of long COVID patients and outcomes is performed, covering patient-reported outcomes, complete pulmonary function tests, physical activity, sleep efficiency and muscle strength.
- ⇒ This trial has an open-label design inherent to the type of intervention and pragmatic design involving PR by real-world primary care physiotherapists, however, the primary outcome measure (6-minute walk distance) is performed by a blinded assessor.

in peer-reviewed publications and presentations at international scientific meetings.

**Trial registration number** NCT05244044.

## INTRODUCTION

### Background and rationale

COVID-19 is an infectious condition caused by the SARS-CoV-2 that was declared a pandemic by WHO in March 2020. Although it can affect multiple organs, respiratory symptoms and pneumonia are the most important manifestations in terms of frequency and severity of the disease. A large observational cohort study in the Netherlands compared persistent symptoms in COVID-19-positive

participants at 90–150 days after COVID-19 with symptoms before COVID-19 and with matched controls and found that in 12.7% of patients, these symptoms could be attributed to COVID-19.<sup>1</sup> Long-term effects of COVID-19 are also referred to as long COVID. The National Institute of Health and Care Excellence (NICE) has defined long COVID as ‘signs and symptoms that develop during or after an infection consistent with COVID-19, that continue for more than four weeks and are not explained by an alternative diagnosis’.<sup>2,3</sup> This includes both definitions of ongoing symptomatic COVID-19 (signs and symptoms for 4 up to 12 weeks) and post-COVID-19 syndrome (signs and symptoms of 12 weeks or longer).<sup>2</sup> It is a global problem with a high economic impact due to absenteeism, loss of productivity, increased healthcare expenditure and other costs.<sup>4</sup>

The most commonly reported long-term symptoms include fatigue, dyspnoea, muscle weakness, anxiety, depression and sleep difficulties with an impact on activities of daily life, mental and physical health and (social) functioning.<sup>5–9</sup> These multisystemic symptoms can persist for months, ranging from mild to incapacitating.<sup>10</sup> Studies have suggested that pre-existing conditions such as the severity of acute COVID-19 (with or without hospitalisation<sup>11,12</sup>), female sex, pre-existing asthma, age, hypothyroidism, obesity and hypertension, are predictive for long COVID development.<sup>13,14</sup> However, the pathophysiology of long COVID remains poorly understood, as well as optimal management of these patients. Given that it is a multifactorial condition, the NICE guideline recommends integrated multidisciplinary rehabilitation services, including physiotherapy.<sup>2</sup> However, data on the effectiveness of rehabilitation in patients with long COVID are scarce so far. Pulmonary rehabilitation (PR) has been proven safe and effective in enhancing physical functioning and quality of life in patients with chronic respiratory diseases. Therefore, experts have proposed using the PR model for patients with long COVID.<sup>15</sup> Although some studies suggest that PR may improve exercise capacity, muscle function, symptoms and quality of life of patients with long COVID, some limitations, such as the lack of a control group, prevent us from generalising these results to the long COVID population.<sup>16–19</sup> Therefore, it is unclear whether the improvements are due to the intervention or to the natural course of long COVID.<sup>16,18,19</sup> Another common limitation is the absence of a follow-up period, thereby missing the long-term benefits of PR in patients with long COVID.<sup>18,19</sup> This calls for more RCTs with a control group, recruiting people with different acute COVID-19 severity, considering a follow-up period. Furthermore, since most studies report the effect of interventions in an inpatient or outpatient hospital setting, there is a lack of studies that describe the effect of PR in a primary care setting.

The PuRe-COVID trial will be a pragmatic randomised controlled trial, aiming to assess the effect of a PR programme in primary care on exercise capacity in patients with long COVID as the primary outcome

parameter. In addition, the longer term effects on exercise capacity and symptom burden at 12 weeks (exercise capacity and symptoms) and 24 weeks (symptoms only) follow-up will be identified as well as the predictors of response to a primary care PR programme.

### Trial design

This prospective, pragmatic, parallel-group, randomised, controlled trial will compare a 12 weeks PR programme supervised by a primary care physiotherapist versus control in patients with long COVID. The enrolment started on 19 April 2022. Patients will be screened and tested in two hospitals in Belgium: a tertiary centre Antwerp University Hospital (UZA) in Antwerp and Ziekhuis Oost-Limburg (ZOL) hospital in Genk.

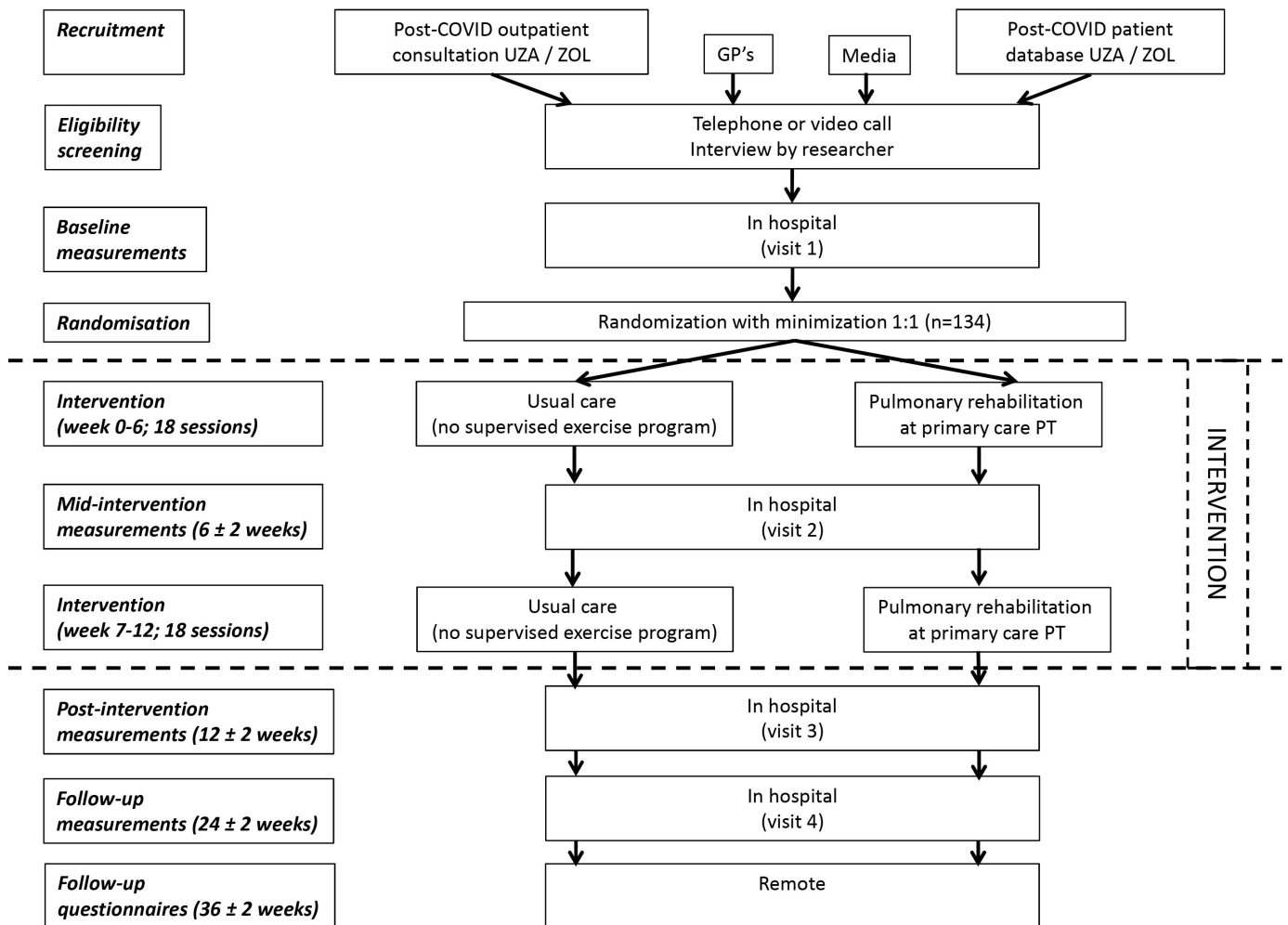
## METHODS AND ANALYSIS

### Study setting

Patients will be recruited through different channels, as shown in figure 1. First, a short eligibility screening will be done by telephone by asking several short questions to quantify symptom burden and eligibility. Subsequently, participants will be assessed during the baseline visit, by a physician involved in the study to check and confirm if the signs and symptoms are due to long COVID, if not, the patient will be a screen failure. All the assessments will be done at one of the two hospitals mentioned above. During the same baseline visit, participants will be randomised to the control or primary care PR intervention group. Follow-up assessments will be performed 6, 12 and 24 weeks after enrolment. Finally, the patient-reported outcomes will be repeated remotely at 36 weeks (table 1).

### Eligibility criteria

Adult patients (age  $\geq 18$  years) will be eligible if they have the post-COVID-19 status (positive COVID-19 PCR test, a positive official pharmacy-performed antigen test, a positive self-performed test confirmed by a physician during the acute COVID-19  $\geq 6$  weeks ago, or positive antibodies prior to vaccination) with persistent COVID-19-related symptoms that were not present or were less severe pre-COVID-19, and evaluated by a physician of the trial. The inclusion criteria related to symptoms are based on the score of four questionnaires: COPD Assessment Test (CAT) $\geq 10$ , or modified Medical Research Council Dyspnoea Scale (mMRC) $\geq 2$  or Checklist Individual Strength (CIS)-fatigue $\geq 36$  or post-COVID-19 Functional Status (PCFS) $\geq 2$ . All patients have to be able to give informed consent and complete the questionnaires. They will be excluded if they have known or self-reported cognitive, hearing, visual, neurological or musculoskeletal conditions that preclude participation in PR. They cannot have followed more than eight physiotherapy sessions in light of their long COVID complaints and none in the past 12 weeks before visit one (randomisation). Additionally, they will not be able to participate if



**Figure 1** Participant flow chart. This figure gives an overview of used recruitment channels and the flow of a patient participating in the trial. GP, general practitioner; PT, physical therapist; UZA, Antwerp University Hospital; ZOL, Ziekenhuis Oost-Limburg.

they have neurological disorders that impact respiratory function, have had any organ transplantation in the past or must undergo any organ transplantation or have an active malignancy or (maintenance) treatment for active malignancy or curatively treated malignancy within the past year.

### Intervention

The control group will not receive any PR or physiotherapist supervised physical activity programme. At the start of this trial, there were no guidelines for the management of long COVID. Recently (December 2022), primary care guidelines for long COVID have been published in Belgium, including physiotherapy, and other forms of support (eg, nutritional, psychological).<sup>20</sup> Patients in the control group are free to follow other treatment options for long COVID. The intervention group will receive a PR programme supervised by a primary care physiotherapist consisting of 36 sessions (three sessions per week for 12 weeks), which includes the following components: education and information about long COVID and a healthy lifestyle, endurance training, (respiratory

muscle strength training, breathing exercises and change towards an active lifestyle, as summarised in [table 2](#).

Patients will be free to choose their physiotherapist, but they will be advised to choose a specialised physiotherapist with experience in PR. The physiotherapists are working in primary care and are not involved in the study as researchers, but only as treating physiotherapists. Education and the experience in PR of the physiotherapist will be captured. Before the start of the intervention, an online meeting with each participating physiotherapist will be organised to inform them about the trial protocol and their funding through the trial budget (for each session given to the patient, for following the start-up meeting and for the extra-administrative burden). They will also receive a digital copy of the concept of the exercise programme outlines. A summarised version for the treatment component of muscle strength training and endurance is shown in [table 3](#).

As postexertional malaise (PEM) has been described in patients with long COVID, all participating physiotherapists will be asked to actively check for PEM every

**Table 1** Overview of measurements and assessments during the trial

	Baseline	Mid-intervention	Postintervention	Follow-up 1	Follow-up 2
Time (weeks)	0	6*	12*	24*	36
Questionnaires					
CAT	X	X	X	X	X
mMRC	X	X	X	X	X
CIS	X	X	X	X	X
PCFS	X	X	X	X	X
Nijmegen	X	X	X	X	X
HADS	X	X	X	X	X
WPAI	X	X	X	X	X
EQ-5D-5L	X	X	X	X	X
Patient interview	X	X	X	X	X
Vital signs, length and weight	X	X	X	X	
Pulmonary evaluation:					
Spirometry+DLCO+lung volumes	X		X	X	
MIP/MEP	X	X	X	X	
Handgrip strength	X	X	X	X	
6MWT	X	X	X	X	
Activity tracker	X	X	X	X	
Pulmonary evaluation: X-ray-thorax/CT-thorax	X				

Assessments during the baseline visit and 6, 12 and 24 weeks visit will be done at one of the two hospitals mentioned above.

Patients in the intervention group must have started pulmonary rehabilitation within 2 weeks after randomisation.

\*Time will start from the date of the first physiotherapy session for the intervention group and the date of randomisation for the control group, considering a range of 2 weeks.

CAT, COPD Assessment Test; CIS, Checklist Individual Strength; DLCO, diffusing capacity for carbon monoxide; EQ-5D-5L, EuroQoL-5D-5L; HADS, Hospital Anxiety and Depression Scale; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; mMRC, modified Medical Research Council Dyspnoea Scale; 6MWT, six-minute walk test; PCFS, post-COVID-19 Functional Status; WPAI, Work Productivity and Activity Impairment Questionnaire.

session. Therefore, the PR programme will consist of five consecutive phases with increasing exercise intensity as described by Salman *et al.*<sup>21</sup> Participating patients will be asked to give a score for the recovery from the previous training session and the intensity of the actual training session, and a total score will be calculated. This score will be seen as an indicator to discuss with the patient whether to proceed to the next phase, or go back to the previous phase, thereby implementing shared decision-making and a staged care approach to prevent PEM.

## Outcomes

### Primary outcome measures

The primary outcome will be the change in exercise capacity measured by 6-minute walk distance (6MWD) between pre-PR and post-PR (baseline to 12 weeks).

### Secondary outcome measures

A secondary outcome measure is a change over time in exercise capacity measured by 6MWD for 24 weeks.

**Table 2** Treatment components

Treatment component	Examples
Information and education	COVID-19 and long COVID, postexertional malaise, active and healthy lifestyle, pacing and coping strategies, sleep hygiene, ...
Muscle strength training	Phased exercise programme, based on RPE scores.
Endurance training	
Respiratory muscle training, breathing exercises	Functional breathing exercises, mucus clearance strategies, relaxation exercises, inspiratory muscle training, ...
This list is not limitative and must be adapted to the patients' need. RPE, rating of perceived exertion.	

**Table 3** Summarised overview of the treatment components of muscle strength training and endurance training

Phase	Examples of exercise intensity	Conditions to be fulfilled before going to the next phase
1 (RPE 6–8)	Prepare to resume physical activity using breathing exercises, stretching, balance exercises, walking.	Follow at least three sessions of phase 1.
2 (RPE 6–11)	Low intensity exercises: walking, light yoga and light ADL tasks with gradual increase of 10–15 min extra per day.	<ul style="list-style-type: none"> <li>▶ Follow at least three sessions of phase 2.</li> <li>▶ Able to walk 30 min on RPE 11.</li> </ul>
3 (RPE 12–14)	Medium-intensity aerobic exercise and more challenging strength exercises (eg, interval exercise).	<ul style="list-style-type: none"> <li>▶ Follow at least three sessions of phase 3.</li> <li>▶ Can accomplish session of 30 min on RPE 12–14.</li> </ul>
4 (RPE 12–14)	More complex aerobic exercises of medium intensity and more challenging with strength exercises that also include coordination and functional elements.	<ul style="list-style-type: none"> <li>▶ Follow at least three sessions of phase 4.</li> <li>▶ ‘Fatigue’ levels are normal.</li> </ul>
5 (RPE>15)	Return to normal ‘baseline’ exercise level.	—

ADL, activities daily life; RPE, rating of perceived exertion.

Predictors of response in 6MWD based on baseline variables will also be analysed.

Additional secondary outcome measures will be change over time in physical activity, objectively measured by an activity tracker (activity intensity and the number of steps) and patient-reported outcomes. The patient-reported outcomes will include the proportion of patients reaching a minimal clinically important difference (MCID) in CAT score, quality of life (EQ-5D-5L) and fatigue (CIS-fatigue).

#### Exploratory outcome measures

Sleep will be an exploratory outcome measure, including total sleep time and sleep efficiency as objectively measured by an activity tracker and subjectively by a sleep diary.<sup>22</sup> Furthermore, changes in scores on the mMRC scale, PCFS, Hospital Anxiety and Depression Scale (HADS), Work Productivity and Activity Impairment Questionnaire (WPAI) and Nijmegen Questionnaire score will be explored. Furthermore, handgrip strength and lung function test variables, including maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), will be considered exploratory outcome measures. In addition, if trial results are positive, the cost-effectiveness of the intervention may be assessed by collecting and analysing healthcare utilisation data from national databases.

#### Participant timeline

Table 1 shows the assessments that will be carried out during the project. Furthermore, demographic and medical details will be recorded for all subjects.

Clinical investigations will include radiology assessments, lung function tests (spirometry, body plethysmography, diffusion capacity, MIP and MEP) (Jaeger MasterScreen, Würzburg, Germany), handgrip strength

and a six-minute walk test (6MWT). Radiology assessment will only be repeated if a chest X-ray or CT-thorax was not performed more than 6 weeks post-COVID-19 infection or was previously abnormal and done >6 weeks ago or at the physician’s discretion.

A standardised patient interview will be performed based on general clinical history taking including but not limited to the date of COVID-19 diagnosis and related disease course during the acute stage (hospitalisation, respiratory support) and after recovery, smoking history, medication use, comorbidities, COVID-19 vaccination status, etc.

Questionnaires will be filled out electronically through a patient interface via a tablet device (during hospital visits) or internet/smartphone web link (on remote) and completed data are automatically feeded into the eCRF. The patients will never be able to see data of the eCRF. Respiratory symptoms will be evaluated using the CAT score and mMRC dyspnoea scale.<sup>23 24</sup> Fatigue will be evaluated through the CIS-fatigue questionnaire.<sup>25</sup> The PCFS scale is a recently developed post-COVID questionnaire to assess functional status and will also be used.<sup>26</sup> Dysfunctional breathing and anxiety and depression symptoms will be evaluated respectively through the Nijmegen questionnaire and HADS.<sup>27</sup> WPAI will be used to assess the impact of health on work and absenteeism from work.<sup>28</sup> Finally, quality of life will be measured using the EuroQol-5D-5L (EQ-5D-5L) questionnaire.<sup>29</sup>

Exercise capacity will be assessed by a blinded tester using a standardised 6MWT protocol in a hallway of 50 m. The 6MWT is a reliable and valid tool for measuring exercise capacity in adults with chronic lung disease. All participants will perform two 6MWTs at baseline, according to American Thoracic Society/European

Respiratory Society standards, with a minimum of 30 min recovery time between the two 6MWTs. The test with the highest 6MWD will be used for analysis.<sup>30</sup> Oxygen saturation monitoring will be part of a 6MWT.

Physical activity will be assessed using a tri-axial activity monitor (Actigraph GT3X BT). This device objectively assesses activity intensity (divided into light, moderate, vigorous and very vigorous intensity activity, using the Freedson Adult VM3 algorithm), number of steps and sleep efficiency (equals total sleep time divided by total time in bed times 100) over 9 days.<sup>22 31</sup> This tracking has been proven accurate and valid for measuring energy expenditure from physical activity in patients with chronic obstructive pulmonary disease (COPD).<sup>32</sup> To the best of our knowledge, no data have been reported on activity duration and sleep efficiency in long COVID patients. A handheld dynamometer (Jamar Smart Digital Hand Dynamometer) will be used to test hand grip strength.

### Sample size

At the time of sample size calculation, no RCT data on (primary care) PR was available in patients with long COVID. Therefore, the sample size calculation is based on Cambach *et al*, where a mean change in 6MWD from baseline to 3 months was +58 m (SD=77, n=23) in the rehabilitation group and +19 m (SD=60, n=24) in the control group in patients with COPD.<sup>33</sup> A Two-Sample T-Test Power Analysis was used to calculate the sample size, based on a power of 0.8 and an alpha of 0.05 and the expected difference after 3 months in 6MWD and SD as reported by Cambach *et al* in COPD patients who received a community-based PR programme compared with a control group.<sup>33</sup> This yielded a sample size of 51 participants in each group. Considering a drop-out rate of 23%, as Fischer *et al* reported, each group's sample size was set at 67 participants.<sup>34</sup> The currently available observational uncontrolled study of Gloeckl *et al* on rehabilitation in post-COVID-19 patients reported similar spread estimates and even a larger effect on the outcome. Hence, the described sample size is expected to be adequate.<sup>18</sup>

### Recruitment

Recruitment will be done at the respiratory outpatient clinics of the two hospitals (UZA, Antwerp, Belgium and ZOL, Genk, Belgium), primary care (general practitioners (GP) and physiotherapists) and via advertisements (social media, posters, publications and a website [www.purecovid.be](http://www.purecovid.be)), as previously shown in [figure 1](#). Recruitment has started in April 2022 and is planned to end in December 2023.

### Assignment of interventions

#### Allocation

Stratification will be done based on hospitalisation during the acute phase (yes, no), 6MWD (<350 m, ≥350 m) and recruitment site. A minimisation procedure (biased coin randomisation) will be used, using a web-based randomisation system QMinim, a dynamic allocation method. If the

screening and collection of baseline data are completed, the study coordinator will perform the stratified randomisation using QMinim and fill in the allocated treatment in the eCRF, REDCap. There will be no need to access randomisation codes in case of an emergency as the trial will be open label. Hence, treatment will be known by the patient and treating physician and recorded in REDCap.

#### Blinding

Due to the nature of the intervention, blinding the patient and the complete study team will not be possible. However, the measurements of the primary endpoint (6MWD) will be performed by a blinded assessor who will not be aware of the intervention allocation of the subjects. This person will be a lung function laboratory or PR team member experienced in performing 6MWT. Therefore, patients will be instructed not to inform this person of their intervention allocation.

#### Data collection, management and monitoring

All participating sites will use the eCRF system REDCap to collect individual pseudonymised patient data. It will not be used as a primary data source except for trial-related questionnaires that the patient will complete electronically. Any adverse event related to the intervention will be well captured by the study coordinator and followed up with the team. The trial will be monitored by sponsor employees but independent of the trial team.

#### Trial management

The Trial Management Group (TMG) will perform day-to-day trial management and will meet frequently. The Trial Steering Committee (TSC) will provide the trial's overall supervision, monitor trial progress and advise on scientific credibility. The TSC will consider and act as appropriate, ultimately taking responsibility for deciding whether the trial needs to be stopped due to safety or efficacy issues. The TSC will meet on average three times during the first year and twice a year after that.

#### Data analysis

Baseline data and patient characteristics will be reported per group. For the primary outcome analysis, a linear mixed model using all available 6MWD measurements over the 24 weeks with the subject as the random effect will be used under the missing at random assumption. The mixed model will then be used to estimate the treatment effect between the two groups at 12 weeks. Different sensitivity analyses will evaluate the treatment effect at 12 weeks. The linear mixed model will add confounders like age, gender, Body Mass Index (BMI), smoker status, asthma, COPD, diabetes and heart disease. A mixed model with multiple imputations by chained equations will be considered. In the imputation model treatment, age, gender, BMI, asthma, COPD, diabetes, heart disease and the available 6MWD measurements will be used. The primary outcome will also be studied in the per-protocol population defined as a compliance rate of 70% (minimum of 25 sessions out of 36). For the secondary

outcomes, physical activity (activity tracker) and patient-reported outcomes (CAT score, EQ-5D-5L, CIS-fatigue score), a linear regression model will be used with the measurement at 12 weeks as an outcome and the treatment and measurement at baseline as predictors. The model will be adjusted for confounders.

The same model can be explored with the change between baseline and 12 weeks as an outcome. The percentage of patients with a significant improvement in CAT, EQ-5D-5L and CIS will be compared between the treatment groups using a  $\chi^2$  test. The MCID used for CAT will be two units,<sup>35</sup> the mean anchor estimates of the minimum important difference for utility index and EQ-Visual Analogue Scale will be 0.051 and 6.9, respectively,<sup>36</sup> and the MCID will be 9.3 units for the CIS fatigue.<sup>37</sup> A logistic regression model will be considered to find predictors of response in 6MWD (an MCID of 30.5 m will be used),<sup>38</sup> like baseline symptom scores (CAT, mMRC and CIS), baseline 6MWD and hospitalisation. For the outcomes measured at multiple visits, a linear mixed model can be used to compare the evolutions over time between the treatment groups. The long-term effect (at 24 and 36 weeks) will be studied with this model and compared with the short-time effect (12 weeks). The exploratory patient-reported outcomes and sleep will be analysed similar to the secondary patient-reported outcomes. In an exploratory analysis, outcomes at 6 weeks (short-term) will be compared with 12 weeks (long-term PR) outcomes.

### Public and patient involvement

During the writing of the protocol, the Flanders long COVID patient association and patients from our clinic have been consulted. In addition, a patient with long COVID is included in our TSC and will be invited to each meeting.

## ETHICS AND DISSEMINATION

### Research ethics approval

Ethical approval was obtained from the institutional review board on 21 February 2022 (Antwerp University Hospital, no. 2022-3067) and on 1 April 2022 (Ziekenhuis Oost-Limburg in Genk, no. Z-2022-01). This protocol describes version 1.6. Any amendment to this protocol version will be sent to the ethics committee for approval before implementation. The results of this trial will be published in peer-reviewed scientific journals, presented at relevant academic conferences and disseminated via the internet and social media. In addition, articles in Layman's wording will be issued.

### Consent or assent and confidentiality

Informed consent will always be obtained before any trial-related investigation. Furthermore, the consent procedure will be compliant with the ICH-GCP guidelines and in line with the requirements of the Belgian Privacy Act of 30 July 2018 on the protection of privacy concerning the

processing of personal data and the European Regulation 2016/679 of 27 April 2016 on the protection of natural persons concerning the processing of personal data and the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation).

### Access to data

The individual anonymised data collected during the trial, the trial protocol, the statistical analysis plan, the informed consent form and the clinical trial report will be shared with qualified researchers engaging in independent scientific research. Data requests can be submitted to [purecovid@uza.be](mailto:purecovid@uza.be) starting after the publication of the primary endpoint and either publication of the follow-up data article or 1 year after the clinical trial report is provided to the funder, whichever happens, earlier. The data will be made accessible for up to 24 months. Extensions will be considered on a case-by-case basis.

### Author affiliations

- <sup>1</sup>Department of Rehabilitation Sciences and Physiotherapy (MOVANT), University of Antwerp, Antwerpen, Belgium
- <sup>2</sup>Clinical Trial Center, University Hospital Antwerp, Edegem, Belgium
- <sup>3</sup>REVAL—Rehabilitation Research Center, Faculty of Rehabilitation Sciences, BIOMED Biomedical Research Institute, Hasselt University, Hasselt, Belgium
- <sup>4</sup>Department of Pulmonary Medicine, University Hospital Antwerp, Edegem, Belgium
- <sup>5</sup>Department of Pulmonary Medicine, Ziekenhuis Oost-Limburg, Genk, Belgium
- <sup>6</sup>Faculty of Medicine and Life Science, Hasselt University, Hasselt, Belgium
- <sup>7</sup>Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Antwerpen, Belgium

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Consent obtained directly from patient(s).

**Provenance and peer review** Not commissioned; externally peer reviewed.

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## ORCID iD

Tess Volckaerts <http://orcid.org/0000-0003-4490-5381>

## REFERENCES

- 1 Ballering AV, van Zon SKR, olde Hartman TC, *et al.* Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *The Lancet* 2022;400:452–61.
- 2 NICE, the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP). *COVID-19 rapid guideline: managing the long-term effects of COVID-19*. 2020.
- 3 Sivan M, Taylor S. NICE guideline on long Covid. *BMJ* 2020;371:m4938.
- 4 Cutler DM. The costs of long COVID. *JAMA Health Forum* 2022;3:e221809.
- 5 Zapatero DC, Hanquet G, Van denK. Epidemiology of long COVID: a pragmatic review of the literature. In: *COVID 19 – KCE Contributions*. 2021.
- 6 Huang C, Huang L, Wang Y, *et al.* 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021;397:220–32.
- 7 Shah W, Hillman T, Playford ED, *et al.* Managing the long term effects of COVID-19: summary of NICE, SIGN, and RCGP rapid guideline. *BMJ* 2021;372:136.
- 8 Antoniou KM, Vasarmidi E, Russell A-M, *et al.* European respiratory society statement on long COVID-19 follow-up. *Eur Respir J* 2022;60:2102174.
- 9 Davis HE, Assaf GS, McCorkell L, *et al.* Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine* 2021;38:101019.
- 10 Greenhalgh T, Knight JM, A’Court C, *et al.* Management of post-acute COVID-19 in primary care. *BMJ* 2020;m3026.
- 11 Townsend L, Dowds J, O’Brien K, *et al.* Persistent poor health after COVID-19 is not associated with respiratory complications or initial disease severity. *Ann Am Thorac Soc* 2021;18:997–1003.
- 12 O’Mahoney LL, Routen A, Gillies C, *et al.* The prevalence and long-term health effects of long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. *EClinicalMedicine* 2023;55:101762.
- 13 Meys R, Delbressine JM, Goërtz YMJ, *et al.* Generic and respiratory-specific quality of life in non-hospitalized patients with COVID-19. *JCM* 2020;9:3993.
- 14 Chen C, Hauptert SR, Zimmermann L, *et al.* Global prevalence of post-Coronavirus disease 2019 (COVID-19) condition or long COVID: A meta-analysis and systematic review. *J Infect Dis* 2022;226:1593–607.
- 15 Spruit MA, Holland AE, Singh SJ, *et al.* COVID-19: interim guidance on rehabilitation in the hospital and post-hospital phase from a European respiratory society and American Thoracic society-coordinated International task force. *Eur Respir J* 2020;56:2002197.
- 16 Nambi G, Abdelbasset WK, Alrawaili SM, *et al.* Comparative effectiveness study of low versus high-intensity aerobic training with resistance training in community-dwelling older men with post-COVID 19 Sarcopenia: A randomized controlled trial. *Clin Rehabil* 2022;36:59–68.
- 17 Li J, Xia W, Zhan C, *et al.* A Telerehabilitation programme in post-discharge COVID-19 patients (TERECO): a randomised controlled trial. *Thorax* 2022;77:697–706.
- 18 Gloeckl R, Leitl D, Jarosch I, *et al.* Benefits of pulmonary rehabilitation in COVID-19: a prospective observational cohort study. *ERJ Open Res* 2021;7:00108–2021.
- 19 Nopp S, Moik F, Klok FA, *et al.* Outpatient pulmonary rehabilitation in patients with long COVID improves exercise capacity, functional status, Dyspnea, fatigue, and quality of life. *Respiration* 2022;101:593–601.
- 20 Hannelore Dillen GB, Bastiaens A, Li A, *et al.* Richtlijn ‘Opvolging en Revalidatie Van Patiënten met Aanhoudende Klachten NA COVID-19 in de Eerste Lijn. In: *volksgezondheid F, ed. Belgisch Centrum voor Evidence-Based Medicine (CEBAM)*. 2022.
- 21 Salman D, Vishnubala D, Le Feuvre P, *et al.* Returning to physical activity after COVID-19. *BMJ* 2021;372:m4721.
- 22 Schutte-Rodin S, Broch L, Buysse D, *et al.* Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* 2008;4:487–504.
- 23 Santus P, Tursi F, Croce G, *et al.* Changes in quality of life and dyspnoea after hospitalization in COVID-19 patients discharged at home. *Multidiscip Respir Med* 2020;15:713.
- 24 Daynes E, Gerlis C, Briggs-Price S, *et al.* COPD assessment test for the evaluation of COVID-19 symptoms. *Thorax* 2021;76:185–7.
- 25 Van Herck M, Goërtz YMJ, Houben-Wilke S, *et al.* Severe fatigue in long COVID: web-based quantitative follow-up study in members of Online long COVID support groups. *J Med Internet Res* 2021;23:e30274.
- 26 Klok FA, Boon GJAM, Barco S, *et al.* The post-COVID-19 functional status scale: a tool to measure functional status over time after COVID-19. *Eur Respir J* 2020;56:2001494.
- 27 Snaith RP. Health and quality of life outcomes 2003;1:29. *Health Qual Life Outcomes* 2003;1:29.
- 28 Reilly MC, Zbrozek AS, Duker EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353–65.
- 29 Janssen MF, Bonsel GJ, Luo N. Is EQ-5D-5L better than EQ-5D-3L? A head-to-head comparison of descriptive systems and value SETS from seven countries. *Pharmacoeconomics* 2018;36:675–97.
- 30 Holland AE, Spruit MA, Troosters T, *et al.* An official European respiratory society/American Thoracic society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014;44:1428–46.
- 31 Sasaki JE, John D, Freedson PS. Validation and comparison of Actigraph activity monitors. *J Sci Med Sport* 2011;14:411–6.
- 32 Rabinovich RA, Louvaris Z, Raste Y, *et al.* Validity of physical activity monitors during daily life in patients with COPD. *Eur Respir J* 2013;42:1205–15.
- 33 Cambach W, Chadwick-Straver RV, Wagenaar RC, *et al.* The effects of a community-based pulmonary rehabilitation programme on exercise tolerance and quality of life: a randomized controlled trial. *Eur Respir J* 1997;10:104–13.
- 34 Fischer MJ, Scharloo M, Abbink JJ, *et al.* Drop-out and attendance in pulmonary rehabilitation: the role of clinical and Psychosocial variables. *Respiratory Medicine* 2009;103:1564–71.
- 35 Smid DE, Franssen FME, Houben-Wilke S, *et al.* Responsiveness and MCID estimates for CAT, CCQ, and HADS in patients with COPD undergoing pulmonary rehabilitation: A prospective analysis. *J Am Med Dir Assoc* 2017;18:53–8.
- 36 Nolan CM, Longworth L, Lord J, *et al.* The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness and minimum important difference. *Thorax* 2016;71:493–500.
- 37 Rebelo P, Oliveira A, Andrade L, *et al.* Minimal clinically important differences for patient-reported outcome measures of fatigue in patients with COPD following pulmonary rehabilitation. *Chest* 2020;158:550–61.
- 38 Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract* 2017;23:377–81.