BMJ Open  Randomised, controlled, open-label pragmatic trial evaluating changes in functional exercise capacity after primary care Pulmonary REhabilitation in patients with long COVID: protocol of the PuRe-COVID trial in Belgium

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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 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-19.1 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’.2 3 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).5 It is a global problem with a high economic impact due to absenteeism, loss of productivity, increased healthcare expenditure and other costs.4

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.5–9 These multisystemic symptoms can persist for months, ranging from mild to incapacitating.10

Studies have suggested that pre-existing conditions such as the severity of acute COVID-19 (with or without hospitalisation),11 12 female sex, pre-existing asthma, age, hypothyroidism, obesity and hypertension, are predictive for long COVID development.13 14 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.5 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.15 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.16–19 Therefore, it is unclear whether the improvements are due to the intervention or to the natural course of long COVID.16 18 19 Another common limitation is the absence of a follow-up period, thereby missing the long-term benefits of PR in patients with long COVID.18 19 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 Ziekenhuis 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 ≥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 ≥26 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)≥10, or modified Medical Research Council Dyspnoea Scale (mMRC)≥2 or Checklist Individual Strength (CIS)-fatigue≥36 or post-COVID-19 Functional Status (PCFS)≥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
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). 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
session. Therefore, the PR programme will consist of five consecutive phases with increasing exercise intensity as described by Salman et al.21 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 1  Overview of measurements and assessments during the trial

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Baseline</th>
<th>Mid-intervention</th>
<th>Postintervention</th>
<th>Follow-up 1</th>
<th>Follow-up 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>mMRC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CIS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PCFS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nijmegen</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HADS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>WPAI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>EQ-5D-5L</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patient interview</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vital signs, length and weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pulmonary evaluation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spirometry+DLCO+lung volumes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIP/MEP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Handgrip strength</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>6MWT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Activity tracker</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pulmonary evaluation: X-ray-thorax/CT-thorax</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

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.

Table 2  Treatment components

<table>
<thead>
<tr>
<th>Treatment component</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information and education</td>
<td>COVID-19 and long COVID, postexertional malaise, active and healthy lifestyle, pacing and coping strategies, sleep hygiene, …</td>
</tr>
<tr>
<td>Muscle strength training</td>
<td>Phased exercise programme, based on RPE scores.</td>
</tr>
<tr>
<td>Endurance training</td>
<td></td>
</tr>
<tr>
<td>Respiratory muscle training, breathing exercises</td>
<td>Functional breathing exercises, mucus clearance strategies, relaxation exercises, inspiratory muscle training, …</td>
</tr>
</tbody>
</table>

This list is not limitative and must be adapted to the patients’ need. 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.22 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 fed 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.23 24 Fatigue will be evaluated through the CIS-fatigue questionnaire.25 The PCFS scale is a recently developed post-COVID questionnaire to assess functional status and will also be used.26 Dysfunctional breathing and anxiety and depression symptoms will be evaluated respectively through the Nijmegen questionnaire and HADS.27 WPAI will be used to assess the impact of health on work and absenteeism from work.28 Finally, quality of life will be measured using the EuroQol-5D-5L (EQ-5D-5L) questionnaire.29

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. 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. This tracking has been proven accurate and valid for measuring energy expenditure from physical activity in patients with chronic obstructive pulmonary disease (COPD). 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. 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. 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. The currently available observational uncontrolled study of Glöckl 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.

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), 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,35 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,36 and the MCID will be 9.3 units for the CIS fatigue.37 A logistic regression model will be considered to find predictors of response in 6MWD (an MCID of 30.5 m will be used),38 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 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.

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**Contributors**

TSL, TV, CB, DR and TV conceived the study concept and design. TSL, DV, CB, DR and TV conceived the study concept and design.

**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.

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**Disclaimer**

Antwerp University Hospital (UZA) shall act as sponsor of the trial. UZA shall act as sponsor of the trial.

**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.

**Open access**

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