PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol of the PuRe-COVID trial in Belgium: a randomized, controlled, open-label pragmatic trial evaluating changes in functional exercise capacity after primary care PUlmonary REhabilitation in patients with long COVID.
AUTHORS	Volckaerts, Tess; Vissers, Dirk; Burtin, Chris; Van Meerbeeck, Xavier; de Soomer, Kevin; Oostveen, E; Claes, Kim; Roelant, Ella; Verhaegen, Iris; Thomeer, Michiel; Criel, Maarten; Quadflieg, Kirsten; Cops, Dries; Ruttens, David; Lapperre, Thérèse S.

VERSION 1 – REVIEW

REVIEWER	Contreras-Briceno, Felipe Pontificia Universidad Católica de Chile, Health of Science
REVIEW RETURNED	27-Dec-2022

GENERAL COMMENTS	Thanks for the opportunity to review this manuscript. It is an interesting RCT multicenter study, with outcomes directed to primary care (exercise capacity as distance obtained at 6MWD-test and other questionnaires). You complete all the items incorporated in the international guidelines. Perhaps, the statistical test mentioned (mixed model) could need profound thinking, considering that you did not mention what will you do if baseline measurements found statistical differences in the main outcome (e.g., ANCOVA test to correct baseline differences ¿?). The rest is OK. Good luck with your study.

REVIEWER	Oliveira, Luis UniEVANGELICA Centro Universitario de Anapolis
REVIEW RETURNED	10-Jan-2023

GENERAL COMMENTS	The study protocol is very well written. The objectives are well defined and the methodology is adequate. The statistical treatment is well described. The protocol is based on up-to-date scientific literature and it is an extremely important topic due to the large number of post-COVID-19 patients worldwide. Pulmonary Rehabilitation emerges as a great and unique option for recovering the functional capacity and quality of life of these patients.

REVIEWER	Declerq, Pierre-Louis hopital de Dieppe, Service de Médecine Intensive Réanimation
REVIEW RETURNED	14-Mar-2023

GENERAL COMMENTS	Thank you for offering me the opportunity to review this protocol which purpose is to evaluate the impact of primary care pulmonary rehabilitation on exercise capacities in patients with long COVID. Long COVID is a major problem that could be considered to a public health concern because of its high frequency and its burden for society. The study protocol is well designed in a pragmatic manner using primary care “in real-life setting” in order to bring some answers to a major concern that could be directly applied for patients’ benefit. Although, I would like to highlight some major and minor concerns. Major 1-The study is considered by the authors as a multicenter study as it’s indicated in the title of the protocol, but I have some reservations for the use of this term. There are only 2 centers involved in the study and the authors can say that it is effectively a multicenter study, however taking into account the interpretation of the results, it's not right. Due, for example, to the possibility of results extrapolation to other regions or countries. So, I think that the terms "2-centers" are more appropriated. 2-The definition of long COVID is essential in that study but I find that the difference between the different terms used to described the post-acute COVID-19 manifestations (i.e long COVID, post COVID syndrome, post COVID-19 condition) are not clear and need to be clarified. Furthermore, it is important to explain to which definition refers long COVID in this manuscript. The authors pointed out that long COVID could be associated to the acute phase of the disease but i don’t think it is suitable to the study. 3-Line 49, p15. The authors indicate that patients were evaluated by a physician regarding persistent post COVID symptoms, but we have no information on the physician (involved or not in the research?) and when this evaluation is performed (before or during the visit 1?). Could you please clarify this point? 4-Line 19, p16. It is important for the results interpretation to know precisely what will be done in terms of health care in each group. So, could you briefly explain what will be "the standard of care for long COVID in Belgium" in the control group? Does it correspond to a specific intervention (like nutritional or psychological support) or controlled patients will only have usual care in primary care setting after a consultation with the attending physician? Are there any health care recommendations in Belgium for long COVID, if yes, could you add it using a reference? 5-Page 16. We have at disposal little informations on the intervention. what is education and information the authors are talking about? Is there psychologic or nutritional support? The details on the PR could be added by using a table for example. 6-Line 30, p16. Patients enrolled in the study are free to choose their physiotherapist as they probably do in primary care when they need physiotherapy care. Although, how to get sure that the physiotherapist has enough skills in PR to achieve the protocol rehabilitation? Furthermore, they will probably be some protocol data to collect corresponding to the PR program but we don’t know

	who is going to complete these data. If it is the physiotherapist's responsibility, we don't know what is his experience in clinical research. In other words, they will probably be some discrepancies regarding the PR between patients in intervention group. I understand it is a pragmatic protocol implemented in primary care and that all the physiotherapists will have an online meeting before PR, but could the authors clarify the physiotherapists position concerning their PR experience, their role in the research and the possible financial interest. Additionally, we don't know how the PR is funded. Minor 1-In the Introduction line 12, p9. The authors declares that COVID-19 is an "infectious multi-organ condition". I agree but I think the respiratory symptoms and pneumonia are the most important manifestations in terms of frequency and severity of the disease, it could be pointed out in the text. Furthermore, the protocol is based on a PR program and the result of 6MWT, like it is used in evaluation and treatment of chronic respiratory disease (COPD). 2-The format of references 4 and 5 is not appropriated. 3-When the authors indicate that "the pathophysiology of long COVID remains poorly understood" (line 53, p9), it can be added (with a reference) that there is no link between the risk of developing long COVID and the initial severity of the disease. This point is important due to the fact that patients involved in the study may or may not have a severe acute COVID possibly requiring a hospitalization. 4- The last paragraph of the introduction could be refined by indicating the hypothesis and the primary and secondary objectives without going into the details of the Methodology section and by exposing the study qualities (advantages) in a Discussion section. 5-Line 12, p14. The authors indicate that a "short eligibility screening will be done". I think that the screening criteria could be added briefly. 6-Figure 1. The visit 1 correspond to a selection visit, this can be added to reinforce the difference between selection and intervention phases. 7-Line 42, p15. The word "positive" is missing when talking about tests result (antigen, self-performed). 8-Line 3, p16. For the comprehension of the sentence could you add "before visit 1 (or randomization)" at the end of the sentence "in the past twelve weeks". 9-Line 8, p16. Could you explain briefly, why organ transplantation and active neoplasia are conditions of study exclusion. Is it in order to not interfere with the disease follow-up? 10-Line 11, p19. Regarding physical activity assessed by an activity monitor, can you explain briefly how the intensity of the

	daily activity is measured? It is the same for sleeping efficiency evaluation, we don't know what is measured. 11-Line 56, p20. Concerning data collection, authors indicate that patients will complete questionaries electronically directly on the e-crf, meaning that patients will have access to the e-crf and potentially have an access to the data not corresponding to the questionaries. Could you clarify that point please?

VERSION 1 – AUTHOR RESPONSE

Responses to the comments from reviewer 1:
We thank the reviewer for his or her positive criticism. A response to the comments is the following:

Perhaps, the statistical test mentioned (mixed model) could need profound thinking, considering that you did not mention what will you do if baseline measurements found statistical differences in the main outcome (e.g., ANCOVA test to correct baseline differences ¿?).
- As the study is randomized any baseline differences are due to chance, baseline will be included in the outcome variable of the mixed model and we can consider constrained longitudinal analysis (constraining means of baseline to be equal between arms) which according to Coffman et al. (2016) yields efficient treatment effect estimates and robust inferential statistics under reasonable missing data assumptions and may be regarded as a generalization of ANCOVA. This is also discussed in Fitzmaurice et al. (2004) where they argue that retaining baseline as part of the outcome is completely equivalent to the strategy where the outcome is restricted to measurements obtained post-baseline and including the baseline as covariate and that the constrained longitudinal analysis is the most powerful. Constrained longitudinal analysis will be added to the sensitivity analysis in the Statistical Analysis Plan.

References:
-Coffman, C.J., Edelman, D., Woolson R.F. (2016) To condition or not condition? Analysing 'change' in longitudinal randomised controlled trials. BMJ Open doi: 10.1136/bmjopen-2016-013096.
-Fitzmaurice G.M., N.M.Laird, J.H. Ware. (2004). Applied longitudinal analysis. John Wiley & Sons. Hoboken, New Jersey.

Responses to the comments from reviewer 3:
We thank the reviewer for his or her detailed comments. We have changed the manuscript accordingly. A point-by-point response is the following:

Major

1-The study is considered by the authors as a multicenter study as it's indicated in the title of the protocol, but I have some reservations for the use of this term. There are only 2 centers involved in the study and the authors can say that it is effectively a multicenter study, however taking into account the interpretation of the results, it's not right. Due, for example, to the possibility of results extrapolation to other regions or countries. So, I think that the terms "2-centers" are more appropriated.
- We agree with this concern and we have corrected the title of the study. As the intervention is performed by multiple primary care physiotherapists, and only the outcome measurements are evaluated in two centers, we regarded the study not completely being a two-center study. We have therefore decided to delete this from the title.

2-The definition of long COVID is essential in that study but I find that the difference between the different terms used to described the post-acute COVID-19 manifestations (i.e long COVID, post COVID syndrome, post COVID-19 condition) are not clear and need to be clarified.
Furthermore, it is important to explain to which definition refers long COVID in this manuscript. The authors pointed out that long COVID could be associated to the acute phase of the disease but i don't think it is suitable to the study.

- We agree that the definition of long COVID is not really clear since different definitions have been reported in the literature, and have been published after we designed our study. However, in this manuscript long COVID is referred to as signs and symptoms that last for at least 6 weeks after the acute COVID-19 infection, as mentioned in the eligibility criteria (page 13), and are therefore compatible with the definition of the NICE guidelines. To avoid any confusion, we have deleted the definition of the WHO guidelines in the introduction of the manuscript (page 10).

3-Line 49, p15. The authors indicate that patients were evaluated by a physician regarding persistent post COVID symptoms, but we have no information on the physician (involved or not in the research?) and when this evaluation is performed (before or during the visit 1?). Could you please clarify this point?

- If a patient is referred or contacts one of the two sites for the study, a pre-screening will be done by several short questions to quantify symptom burden and eligibility. During the first study visit the patient is screened by a physician involved in the study to check and confirm if the signs and symptoms of the patient are due to long COVID. If not, the patient will be a screen failure (see page 12).

4-Line 19, p16. It is important for the results interpretation to know precisely what will be done in terms of health care in each group. So, could you briefly explain what will be "the standard of care for long COVID in Belgium" in the control group? Does it correspond to a specific intervention (like nutritional or psychological support) or controlled patients will only have usual care in primary care setting after a consultation with the attending physician? Are there any health care recommendations in Belgium for long COVID, if yes, could you add it using a reference?

- We have adapted the description of management of the control group to further clarify this (page 14). At the start of this trial there were no guidelines for the management of long COVID. Recently, (Dillen et al., 2022) primary care guidelines for long COVID have been published in Belgium, including physiotherapy, and other forms of support (e.g. nutritional, psychological). Patients participating in this trial are asked not to follow any PR or supervised physiotherapy, whereas other treatment options are free to follow.

References: Hannelore Dillen GB, Ann Bastiaens, Ann Li, Anne-lies Van den Broeck, Anne-Sophie Spiette, Catharine Vander Linden, Chris Burtin, Daniel Langer, Dominique Van de Velde, Ellen Excelmans, Erika Vanhauwaert, Hadi Waelkens, Johan Wens, Joke Platteeuw, Paul Boon, Pierre Garin, Roy Remmen, Séverine Tibor, Sofie Gijsbers, Stefan Teughels, Stijn De Baets, Thibault Coppens, Yannick Vande Weygaerde, Wim Janssens, Rik Gosselink, Thierry Troosters, Jan Verbake. 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), 2022:66.

5-Page 16. We have at disposal little informations on the intervention. what is education and information the authors are talking about? Is there psychologic or nutritional support? The details on the PR could be added by using a table for example.

- We have now added more details on the PR intervention as follows (see page 14-15). This overview is indicative but not limitative and should be personalized for each patient, it is used as a guideline for the physiotherapists (see page 14). Extra tables are added to provide more information

(see table 2 and 3). At the end of the intervention, physiotherapists are asked which interventions they did with their patient to get a global overview. Since this is a pragmatic trial we don't have a detailed overview of used equipment, frequencies, intensities, etc… for each session.

Table 2: Treatment components.

Treatment component	Examples
Information and education	COVID-19 and long COVID, post exertional malaise, active and healthy lifestyle, pacing and coping strategies, sleep hygiene,…
Muscle strength training	Phased exercise program, based on RPE scores.
Endurance training	
Respiratory muscle training, breathing exercises	Functional breathing exercises, mucus clearance strategies, relaxation exercises, inspiratory muscle training,…

Footnote: This list is not limitative and must be adapted to the patients' need. RPE: rating of perceived exertion.

Table 3: Summarized 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 minutes extra per day.	- Follow at least three sessions of phase 2. - Able to walk 30 minutes on RPE 11.
3	(RPE 12-14) Medium-intensity aerobic exercise and more challenging strength exercises (e.g., interval exercise).	- Follow at least three sessions of phase 3. - Can accomplish session of 30 minutes on RPE 12-14.
4	(RPE 12-14) More complex aerobic exercises of medium intensity and more challenging with strength exercises that also include coordination and functional elements.	- Follow at least three sessions of phase 4. - "Fatigue" levels are normal.
5	(RPE > 15) Return to normal "baseline" exercise level.	/

Footnote: RPE: rating of perceived exertion; ADL: activities daily life.

6-Line 30, p16. Patients enrolled in the study are free to choose their physiotherapist as they probably do in primary care when they need physiotherapy care. Although, how to get sure that the physiotherapist has enough skills in PR to achieve the protocol rehabilitation? Furthermore, they will probably be some protocol data to collect corresponding to the PR program but we don't know who is going to complete these data. If it is the physiotherapist's responsibility, we don't know what is his experience in clinical research. In other words, they will probably be some discrepancies regarding the PR between patients in intervention group. I understand it is a pragmatic protocol implemented in primary care and that all the physiotherapists will have an online meeting before PR, but could the authors clarify the physiotherapists position concerning their PR experience, their role in the research and the possible financial interest. Additionally, we don't know how the PR is funded.

- The physiotherapists are working in primary care and are not involved in the study as researchers, but only as treating physiotherapists. They are referred by the study team because of their known experience or selected by the patient because of practical reasons. We recognize the concerns about their PR experiences, therefore we have implemented a small questionnaire regarding their PR background (see below). We agree that these possible differences in experience may have an impact on the quality of the delivered therapy, but by guiding the patient to a recognized PR physiotherapist, by organizing an online meeting with each participating physiotherapist, and by capturing information about their experience, we aim to keep this to a minimum, also bearing in mind

the pragmatic design of this trial and the current practice in Belgium. All the physiotherapists are paid from the study budget for each session given to the patient, for following the start-up training and for the extra administrative burden, we have amended this in the protocol (see page 15).
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Minor

1-In the Introduction line 12, p9. The authors declares that COVID-19 is an “infectious multi-organ condition”. I agree but I think the respiratory symptoms and pneumonia are the most important manifestations in terms of frequency and severity of the disease, it could be pointed out in the text. Furthermore, the protocol is based on a PR program and the result of 6MWT, like it is used in evaluation and treatment of chronic respiratory disease (COPD).
- We have amended the introduction as suggested by the reviewer (page 10).

2-The format of references 4 and 5 is not appropriated.
- Thank you for noticing this, we have corrected these references (page 10).

3-When the authors indicate that “the pathophysiology of long COVID remains poorly understood” (line 53, p9), it can be added (with a reference) that there is no link between the risk of developing long COVID and the initial severity of the disease. This point is important due to the fact that patients involved in the study may or may not have a severe acute COVID possibly requiring a hospitalization.
- We have adapted the introduction (page 10) so it is more clear that there is no link between the prior hospitalization and long COVID, and so both patients (with or without a hospitalization during their acute COVID-19 infection), can develop long COVID. (1, 2) As clarified in the eligibility criteria, participating patients will have had an acute COVID-19 □ 6 weeks ago.

References:
1. Townsend L, Dowds J, O'Brien K, Sheill G, Dyer AH, O'Kelly B, et al. Persistent Poor Health after COVID-19 Is Not Associated with Respiratory Complications or Initial Disease Severity. Ann Am Thorac Soc. 2021;18(6):997-1003.
2. O'Mahoney LL, Routen A, Gillies C, Ekezie W, Welford A, Zhang A, 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.

4- The last paragraph of the introduction could be refined by indicating the hypothesis and the primary and secondary objectives without going into the details of the Methodology section and by exposing the study qualities (advantages) in a Discussion section.
- We have adapted the introduction (page 11).

5-Line 12, p14. The authors indicate that a “short eligibility screening will be done”. I think that the screening criteria could be added briefly.
- We agree that this could be described more clearly so we have adapted the manuscript (page 12). We will check the in- and exclusion criteria and quantify the symptom burden.

6-Figure 1. The visit 1 correspond to a selection visit, this can be added to reinforce the difference between selection and intervention phases.
- We would like to thank you for sharing your concern. Since the first visit is a selection visit but also the visit of our baseline results and randomization, we have clarified this in the text of the protocol, section “study setting” (page 12).

7-Line 42, p15. The word “positive” is missing when talking about tests result (antigen, self-performed).

- We have added the word “positive” (page 13).

8-Line 3, p16. For the comprehension of the sentence could you add “before visit 1 (or randomization)” at the end of the sentence “in the past twelve weeks”.
- We have implemented this at page 14.

9-Line 8, p16. Could you explain briefly, why organ transplantation and active neoplasia are conditions of study exclusion. Is it in order to not interfere with the disease follow-up?
- Organ transplantation and active neoplasia are conditions of study exclusion because these diseases can produce similar symptoms. 1,2 Therefore, it is not clear in this patient population whether their complaints are caused by long COVID or by this underlying diagnosis.

References:

1. Barsevick AM, Cleeland CS, Manning DC, O'Mara AM, Reeve BB, Scott JA, et al. ASCPRO recommendations for the assessment of fatigue as an outcome in clinical trials. J Pain Symptom Manage. 2010;39(6):1086-99.
2. Bourgeois N, Shallwani SM, Al-Huda FS, Mathur S, Poirier C, Janaudis-Ferreira T. Relationship of Exercise Capacity, Physical Function, and Frailty Measures With Clinical Outcomes and Healthcare Utilization in Lung Transplantation: A Scoping Review. Transplant Direct. 2022;8(11):e1385.

10-Line 11, p19. Regarding physical activity assessed by an activity monitor, can you explain briefly how the intensity of the daily activity is measured? It is the same for sleeping efficiency evaluation, we don’t know what is measured.
- The activity intensity is measured by a tri-axial activity tracker (Actigraph GT3X BT) and it is divided into four different classes: light, moderate, vigorous and very vigorous activity intensity, based on the Freedson Adult VM3 algorithm. This method has been proven to be valid. 1 Sleep efficiency is also measured by the Actigraph GT3X BT and equals total sleep time divided by total time in bed times 100. 2 We have added this in the “participant timeline” (see page 18).

References:

1 Sasaki JE, John D, Freedson PS. Validation and comparison of ActiGraph activity monitors. J Sci Med Sport. 2011;14(5):411-6.
2 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 Oct 15;4 (5):487–504. DOI:10.5664/jcsm.27286

11-Line 56, p20. Concerning data collection, authors indicate that patients will complete questionaries electronically directly on the e-crf, meaning that patients will have access to the e-crf and potentially have an access to the data not corresponding to the questionaries. Could you clarify that point please?
- The patient has no access to data in the eCRF. Questionnaires will be filled out electronically trough an interface via a tablet device (during hospital visits) or internet/smartphone web link (on remote) and completed data is automatically feeded into the eCRF (see page 17). The patients will never be able to see data of the eCRF, they will only see the questionnaires to be completed.

VERSION 2 – REVIEW

REVIEWER	Declerq, Pierre-Louis hopital de Dieppe, Service de Médecine Intensive Réanimation
REVIEW RETURNED	04-May-2023

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. The study protocol is accurate and complete. The answers given and added to the manuscript are appreciable and informative and there is no point left to clarify. Looking forward to know the results of this study. Regards

VERSION 2 – AUTHOR RESPONSE