
Monograph:
Raine, Gary Austin, Khouja, Claire Louise orcid.org/0000-0002-9571-3147, Khatwa, Meena et al. (2 more authors) (2022) Treatment and rehabilitation of Long COVID: a scope of the RCT literature : July 2022. Research Report. EPPI-Centre, Social Science Research Unit, UCL Institute of Education, University College London. , London.

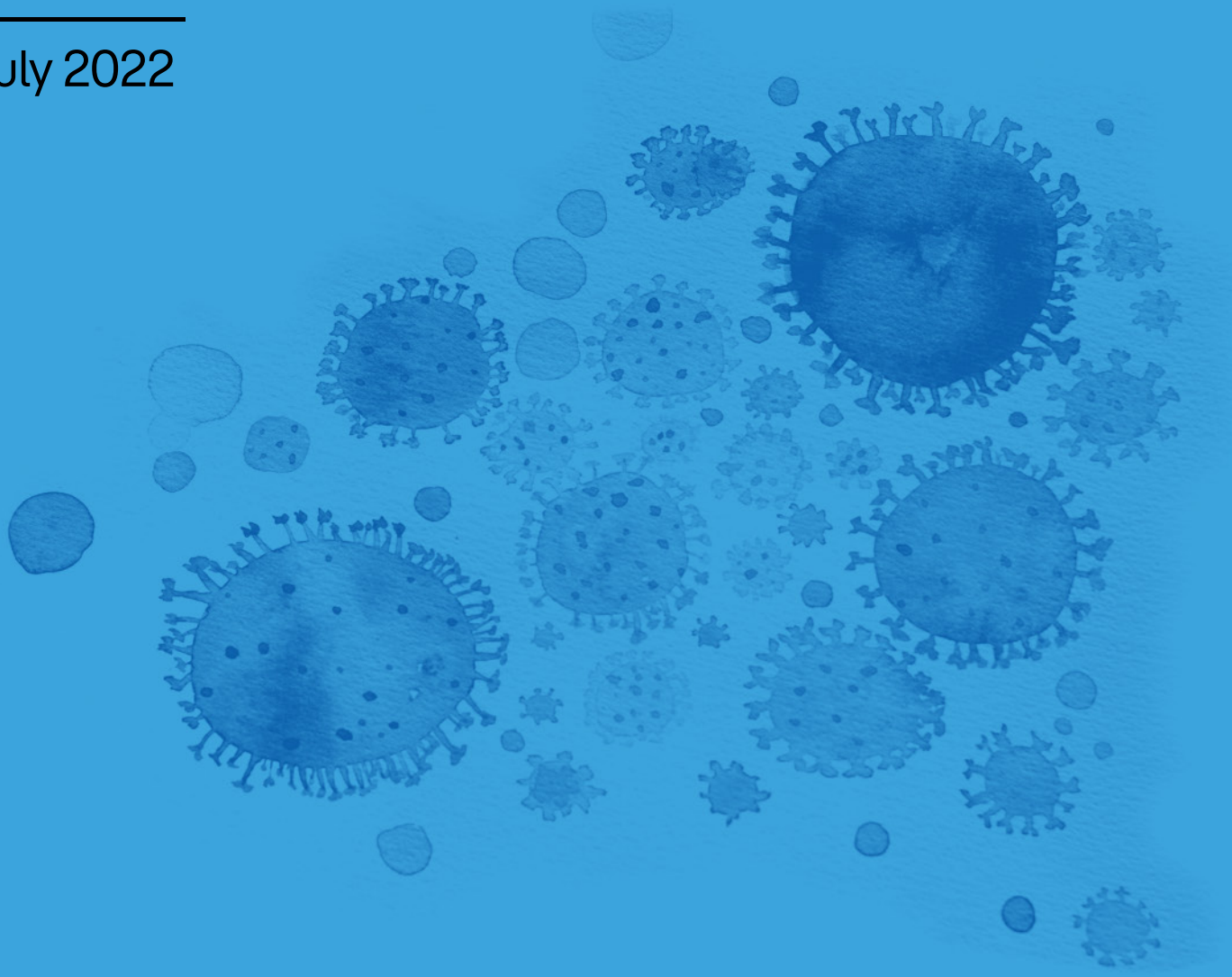
NIHR Policy Research Programme Reviews Facility

To support national policy development and implementation

Treatment and rehabilitation of Long COVID

A scope of the RCT literature

July 2022



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Treatment and rehabilitation of Long COVID: A scope of the RCT literature

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Funding
This review was commissioned by the National Institute for Health Research (NIHR) Policy Research Programme (PRP) for the Department of Health and Social Care (DHSC). It was funded through the NIHR PRP contract with the EPPI Centre at UCL (Reviews facility to support national policy development and implementation, PR-R6-0113-11003). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the DHSC.

Conflicts of interest
There were no conflicts of interest in the writing of this report.

Contributions
The opinions expressed in this publication are not necessarily those of the EPPI Centre or the funders. Responsibility for the views expressed remains solely with the authors.

This report should be cited as:
Raine G, Khouja C, Khatwa M, Sutcliffe K, Sowden A (July 2022) *Treatment and rehabilitation of Long COVID: A scope of the RCT literature.* London: EPPI Centre, UCL Social Research Institute, UCL Institute of Education, University College London.

Editorial & design by: Lionel Openshaw

ISBN: 978-1-911605-31-7

Summary

- We identified 14 randomised controlled trials published in the last six months, which examined the effectiveness of a range of interventions focused on Long COVID treatment or rehabilitation.
- Across trials, the post COVID period ranged widely from a few weeks after symptom onset or diagnosis to several months post recovery from active infection or hospital discharge.
- Trial quality varied and inadequate reporting of methods frequently precluded a full assessment of the risk of bias. However, six trials were rated positively for at least 75% of the domains we assessed.

Introduction

This is the first in an ongoing series of quarterly evidence scans requested by NHS England and the Department of Health and Social Care. It was conducted to identify and quality assess recently published randomised controlled trials (RCTs) evaluating treatment or rehabilitation for Long COVID.

Method

Identification of studies

We searched four main sources to identify relevant studies:

1) Our living systematic map of Long COVID-19 evidence maintained by staff at the London-York NIHR Policy Reviews Facility. We screened all studies categorised as 'Treatment Evaluation' in the map, which were published in the current year (1st January to 1st June 2022).

2) Cochrane Central Register of Controlled Trials (CENTRAL). We searched CENTRAL using a range of key terms that have been used in the literature to describe symptoms and effects persisting beyond the acute stage of COVID infection. Searches were restricted to the current year.

3) Searches covering the three-month period between March and June 2022 were also conducted of PubMed and CINAHL to identify any trials that had not yet been incorporated into CENTRAL. We used identical terms to the search of CENTRAL but also included an appropriate filter for identifying randomised trials.[(1)] The PubMed search was restricted to the title and abstract fields. The full PubMed search strategy and CINAHL randomised controlled trials filter used are provided in Appendix 1, (page 13). No language restrictions were applied to any of the searches.

Study selection

Studies were screened for inclusion against the following criteria:

Population - patients with Long COVID, which we conceptualised broadly as experiencing at least one symptom or effect that persists or develops after acute COVID-19 infection. No restrictions were placed on the socio-demographic characteristics of participants or COVID severity. We also did not apply criteria relating to the time period after acute infection owing to variation in how Long COVID has been defined in the literature.

Interventions - any intervention aimed at treating or rehabilitating patients with Long COVID. This could include, but was not limited to, medication, supplements, and physical therapy.

Outcomes - any outcome related to the effectiveness, cost effectiveness, safety or side effects of interventions. Studies could also report outcomes related to the implementation of interventions.

Study design - prospective trials with random allocation of participants to intervention and comparator groups. When designed and conducted to a high standard, a randomised controlled trial is often the most robust type of primary study design for investigating intervention effectiveness.[2]

Publication type and status - any publication type reporting the findings from a RCT (e.g. full papers, research letters etc.), grey literature and pre-prints were eligible for inclusion. A pre-print is a research paper that has been published online before being peer-reviewed.

Quality assessment

Each study was appraised according to the Joanna Briggs Institute (JBI) Checklist for Randomized Controlled Trials.[3] In contrast to the Cochrane Risk of Bias Tool,[4] the JBI checklist does not require an assessment of bias for specific outcomes. It provides instead a general appraisal of each trial as a whole, which was needed in this piece of work as we were not seeking to extract and synthesise outcomes. Assessments were conducted by one reviewer and checked by another. The appraisal identified potential sources of bias and threats to the validity and reliability of study findings. The full checklist is provided in Appendix 2 (page 15).

Key findings

We screened 112 records and identified 14 RCTs that had been published since January 2022.[5-18] The flow of studies through the process is shown in Appendix 3 (page 16). Table 1 (page 4) presents the aim and key characteristics of the trials.

Interventions and comparators

The trials evaluated the effectiveness of a range of different interventions. Eight trials focused on treatments that involved the consumption, injection or inhalation of various substances – drugs, adaptogens and other supplements, Chinese medicine, molecular Hydrogen, and essential oils.[5-11, 15] Six trials examined various types of physical therapy and training for persistent symptoms such as breathlessness and/or other functional limitations.[12-14, 16-18] Two trials compared different drug dosages or training intensities without using any other comparator groups.[6, 13] All other trials compared the intervention to various types of control group, such as placebo control or usual care. In two trials of tele-rehabilitation, the main difference between the intervention and comparator groups was in the method for delivering information to participants and level of support given to them.[14, 16]

Participants

There was wide variation between trials in relation to time after COVID infection, with some recruiting participants relatively soon after recovery from active infection. For example, one trial recruited a cohort of acute post COVID patients who were experiencing persisting symptoms, on average, 26 days after testing positive.[5] Conversely, all participants in four trials were recruited at least two months after testing negative, recovery or hospital discharge.[7, 9, 12, 14]

Countries

Two of the 14 trials were conducted in the UK;[12, 17] two in the USA;[8, 9] two in India;[6, 18] and two in Turkey.[14, 16] The remaining 6 trials were conducted in China;[15] Czech Republic;[5] Georgia;[10] Italy;[7] Russia;[11] and Saudi Arabia.[13]

Trial quality

Assessments of the trials against the JBI criteria are provided in Table 2 (pages 9 and 10). Only one trial was assessed as having a low risk of bias for all 13 appraisal criteria.[10] A further five met at least ten criteria on the checklist,[7, 9, 13, 16] including one of the UK-based trials.[17] The remaining eight trials gained positive ratings for between four and nine criteria.[5, 6, 8, 11, 12, 14, 15, 18] It is worth noting that the trials reported by Dhooria et al.[6] and Gaylis et al.[8] were published as a research letter and brief report, respectively. These publications are shorter than full papers, which means that there is less information reported about methods on which to make judgements about quality.

Inadequate reporting of key information was a common issue, which meant we often could not determine the risk of bias across multiple domains. For example, for half the trials, we could not tell if an appropriate procedure had been used to prevent the researchers from knowing whether the next patient would be allocated to the treatment or comparator group (allocation concealment)(Q2);[5, 8, 9, 11, 12, 15, 18] or whether outcomes were measured in a reliable way (Q11).[6, 8, 11, 12, 14, 15, 17]

It was also not possible to assess whether researchers in five trials had used an appropriate method of randomisation for allocating participants to treatment groups (Q1);[8, 9, 11, 15, 18] or if they had conducted an appropriate statistical analysis (Q12).[5, 6, 8, 11, 15]

In all but one of the trials,[18] authors reported that intervention and comparator groups were similar at the start of the intervention in terms of key demographic and clinical characteristics (Q3). This is important as the existence of key differences between groups can be a potential source of bias.[3]

There is potentially a high risk of bias when trial participants know whether they are in the intervention or comparator group, and similarly, whether the personnel responsible for delivering the treatment and assessing outcomes of interest are also aware of patients' group allocation. This risk can be minimised if researchers implement a process of blinding.[3] Only two trials received a positive rating for all three criteria relating to the blinding of study participants and trial personnel (Q4, Q5, Q6).[9, 10] Separately, we assessed seven trials positively for the blinding of participants (Q4),[5, 7, 9, 10, 13, 16, 18] and three met the criterion of masking participants' group allocation from those individuals delivering treatment (Q5).[9, 10, 16] In seven of the remaining 11 trials, authors reported that there was no blinding of trial personnel in relation to treatment delivery.[5, 6, 13-15, 17, 18] Finally, the trial personnel who assessed the outcomes of interest were blinded to participants' group allocation in six studies (Q6).[7, 9, 10, 13, 17, 18] The authors of one paper stated that the nature of the intervention in their trial prevented the blinding of study participants.[17] This explanation may also account for the lack of blinding of participants and trial personnel in some of the other trials.

To conclude, this first evidence scan identified a geographically diverse group of 14 RCTs published in the last six months, which examined the effectiveness of a range of interventions focused on the treatment or rehabilitation of people with Long COVID. Across trials, the post COVID period ranged widely from a few weeks after symptom onset or diagnosis to several months post recovery from active infection or hospital discharge. Trial quality varied and inadequate reporting of methodological detail frequently precluded a full assessment of the risk of bias. However, six trials were rated positively for at least 75% of the domains we assessed.

Table 1: Study characteristics

First author Country	Aim of study	Main symptom/ effect experienced	Post COVID time	Participants' gender (n) % female	Primary outcome(s) of interest	Comparator
Botek[5] Czech Republic	To assess the effect of 14 days of molecular Hydrogen inhalation in patients with acute post-COVID-19 syndrome	Unclear/Not reported	21-35 days after positive PCR test	Mixed (50) 48% female	*Pulmonary/respiratory function*: Forced vital capacity (FVC); forced expiratory volume in the first second (FEV1); FEV1/FVC ratio *Physical fitness:* six-minute walking distance; arterial oxygen saturation; rate of perceived exertion; level of dyspnoea *General symptoms/clinical outcomes*: perceptions of fatigue, muscle soreness, dyspnoea, and insomnia	Ambient air
Dhooria[6] India	To compare high-dose versus low-dose prednisolone in symptomatic patients with post-COVID-19 diffuse parenchymal lung abnormalities	Lung abnormalities	3-8 weeks from acute COVID-19 symptom onset. Median 36 days from symptom onset and 15 days since discharge	Mixed (130) 32% female	*Radiological:* complete radiological response (⩾90% reduction in diffuse lung abnormalities)	Comparison of two drug doses only. No other comparator

Di Stadio[7] Italy	To investigate recovery of olfactory function in patients treated with Palmitoylethanolamide and Luteolin supplement (PEA-LUT) oral supplements plus olfactory training versus olfactory training plus placebo	Anosmia/hyposmia	Impairment persisting at least 180 days after negative test	Mixed (185) 65% female	*Olfactory function*	Supplement therapy placebo
Gaylis[8] USA	Exploratory trial treating long COVID with the CCR5-binding antibody leronlimab	General/multiple symptoms	Unclear/not stated	Unclear/Not stated (55)	*General symptoms/ clinical outcomes:* Symptom severity	Saline placebo
Hawkins[9] USA	To evaluate the potential for inhalation of essential oils to improve energy levels among otherwise healthy female survivors of acute COVID-19 who experience a lack of energy more than five months after recovery	Fatigue/lack of energy	Recovery from COVID-19 five or more months before the start of the intervention	Female only (40)	*Physical fitness:* fatigue	Inert, odourless placebo (fractionated coconut oil)
Karosanidze[10] Georgia	To assess the efficacy of adaptogens on the recovery of patients with Long COVID symptoms	General/multiple symptoms - experienced at least three of nine Long COVID symptoms in the 30 days before study recruitment	After discharge. Time since hospitalisation ranged from 11-88 days	Mixed (100) 86% female	*Physical fitness:* physical activity and walking duration *Psychological:* anxiety & depression *General symptoms/ clinical outcomes:* symptom duration and severity; clinical recovery;	Placebo suspension with inactive ingredients & similar appearance, smell & colour

					length of homestay/sick listed *Blood parameters:* hypercoagulation, immune response and inflammatory markers *Cognitive:* attention and memory	
Kharaeva[11] Russia	Attempt to obtain clinical proof of efficacy for two fermented food supplements in the form of syrups based on Carica papaya and Morinda citrifolia	General/multiple symptoms	After hospital discharge (20–40 days after admission)	Mixed (213) 50% female	*General symptoms/ clinical outcomes: f*requency and intensity of a range of physical and psychological symptoms	Honey and water placebo
McNarry[12] UK/Ireland (Wales)	To investigate the potential rehabilitative role of inspiratory muscle training (IMT) for people recovering from COVID-19 who are experiencing prolonged symptoms	Primary symptom of breathlessness	Nine months Post-acute COVID	Mixed (281) 88% female	*Health related quality of life*	Usual care waiting list control
Nambi[13] Saudi Arabia	To investigate the effects of different aerobic training protocols combined with resistance training in community-dwelling older adults with post-COVID-19 sarcopenia symptoms	Post-COVID-19 Sarcopenia (skeletal muscle loss)	Unclear/not stated	Male only (76)	*Physical fitness:* Handgrip strength	Comparison of two training intensities only. No other comparator

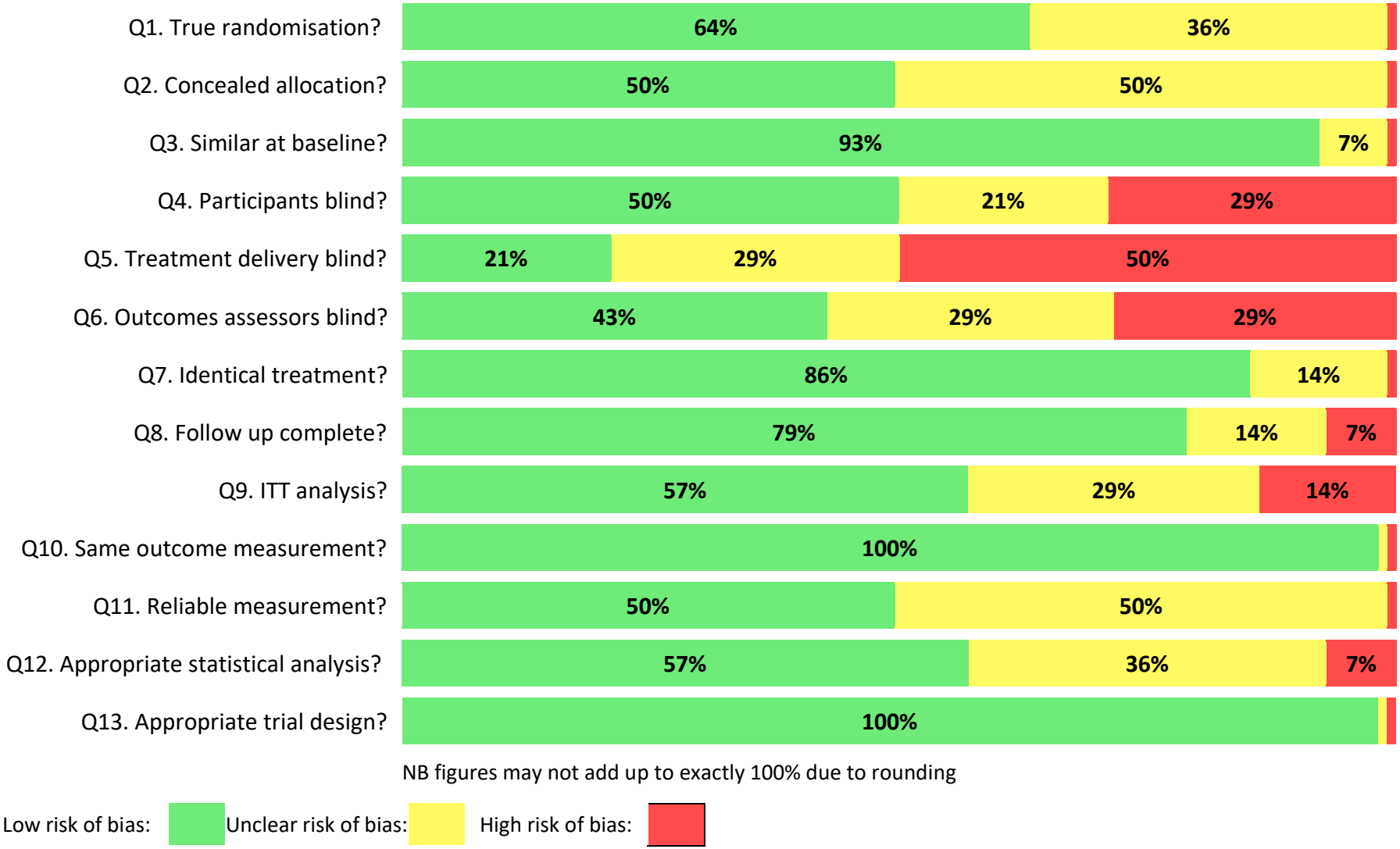
Okan[14] Turkey	To evaluate the effectiveness of breathing exercises given by telemedicine in post-COVID-19 dyspnoeic individuals	Dyspnoea (shortness of breath)	At least 2 months after discharge	Mixed (52) 48% female	*Pulmonary/respiratory function:* FVC, FEV1, FEV1/FVC Ratio, and Maximum Voluntary Ventilation (MVV) *Physical fitness:* six-minute walking distance	Brochure detailing the exercises to be performed
Pang[15] China	To evaluate the effectiveness and safety of Qingjin Yiqi granules (QJYQ) on post-COVID-19 condition	The common symptoms at baseline were breathlessness (29.6%), fatigue (29.6%), chest distress (24.2%), cough (18.3%), insomnia (18%)	Immediately after discharge	Mixed (388) 62% female	*Pulmonary/respiratory function:* dyspnoea	standard rehabilitation treatments
Pehlivan[16] Turkey	To investigate the feasibility and effectiveness of a telerehabilitation exercise programme performed without requiring any special equipment on the physical condition of COVID-19 subjects	Participants had worse physical functions after discharge compared to pre-illness	Participants were in the first 4 weeks after discharge	Mixed (34) 26% female	*Pulmonary/respiratory function:* dyspnoea *Physical fitness:* fatigue; physical performance and activities *Health related quality of life:* impact on overall health, daily life, and perceived well-being *Psychological:* depression	Brochure detailing the exercises to be performed

					General symptoms/ clinical outcomes: pain	
Philip[17] UK/Ireland (England)	To assess whether an online breathing and wellbeing programme improves health related quality of life in people with persisting breathlessness following COVID-19	Ongoing breathlessness, with or without anxiety	At least 4 weeks after symptom onset	Mixed (150) 81% female	Health related quality of life	Usual care
Sharma[18] India	To analyse the effects of a pulmonary tele-rehabilitation programme in COVID-19 outpatients	Respiratory and functional limitations	After discharge – time not stated	Mixed (30) Not reported	*Pulmonary/respiratory function:* dyspnoea *Physical fitness:* Fatigue	Usual care

Table 2: JBI risk of bias assessment

First author (publication year)	Q1. True randomisation?	Q2. Concealed allocation?	Q3. Similar at baseline?	Q4. Participants blind?	Q5. Treatment delivery blind?	Q6. Outcomes assessors blind?	Q7. Identical treatment?	Q8. Follow up complete?	Q9. ITT analysis?	Q10. Same outcome measurement?	Q11. Reliable measurement?	Q12. Appropriate statistical analysis?	Q13. Appropriate trial design?
Botek (2022)	+	?	+	+	-	-	+	+	-	+	+	?	+
Dhooria (2022)*	+	+	+	-	-	-	+	-	?	+	?	?	+
Di Stadio (2022)	+	+	+	+	?	+	+	+	+	+	+	+	+
Gaylis (2022)**	?	?	+	?	?	?	+	?	?	+	?	?	+
Hawkins (2022)	?	?	+	+	+	+	+	+	+	+	+	+	+
Karosanidze (2022)	+	+	+	+	+	+	+	+	+	+	+	+	+
Kharaeva (2022)	?	?	+	?	?	?	+	+	+	+	?	?	+
McNarry (2022)	+	?	+	?	?	?	?	+	+	+	?	+	+
Nambi (2022)	+	+	+	+	-	+	+	+	?	+	+	+	+
Okan (2022)	+	+	+	-	-	-	+	+	+	+	?	+	+
Pang (2022)	?	?	+	-	-	-	+	+	+	+	?	?	+
Pehlivan (2022)	+	+	+	+	+	?	+	+	-	+	+	+	+
Philip (2022)	+	+	+	-	-	+	+	+	+	+	?	+	+
Sharma (2022)	?	?	?	+	-	+	?	?	?	+	+	-	+

*Published as a research letter; **published as a brief report.


Q1. True randomisation?
64%
36%
Q2. Concealed allocation?
50%
50%
Q3. Similar at baseline?
93%
7%
Q4. Participants blind?
50%
21%
29%
Q5. Treatment delivery blind?
21%
29%
50%
Q6. Outcomes assessors blind?
43%
29%
29%
Q7. Identical treatment?
86%
14%
Q8. Follow up complete?
79%
14%
7%
Q9. ITT analysis?
57%
29%
14%
Q10. Same outcome measurement?
100%
Q11. Reliable measurement?
50%
50%
Q12. Appropriate statistical analysis?
57%
36%
7%
Q13. Appropriate trial design?
100%
NB figures may not add up to exactly 100% due to rounding
Low risk of bias:
Unclear risk of bias:
High risk of bias:

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Appendix 1

PubMed search strategy

#1 Long covid [tiab] OR post covid [tiab] OR post acute covid [tiab] OR PASC [tiab] OR long term covid [tiab] OR ongoing covid [tiab] OR chronic covid [tiab]

#2 long term symptom* [tiab] OR long term effect* [tiab] OR persisting symptom*[tiab] OR persistent symptom*[tiab] OR long term sequelae [tiab] OR post discharge [tiab] OR postdischarge [tiab] OR long haul* [tiab] OR post acute sequelae [tiab]

#3 COVID [tiab] OR COVID-19 OR SARS-CoV-2 [tiab]

#4 #2 AND #3

#5 #1 OR #4

#6 randomized controlled trial [pt]

#7 controlled clinical trial [pt]

#8 (randomized [tiab] OR randomised [tiab])

#9 placebo [tiab]

#10 clinical trials as topic [mesh: noexp]

#11 randomly [tiab]

#12 trial [ti]

#13 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

#14 animals [mh] NOT humans [mh]

#15 #13 NOT #14

#16 #5 AND #15

CINAHL RCT filter

#1 MH randomized controlled trials

#2 MH double-blind studies

#3 MH single-blind studies

#4 MH random assignment

#5 MH pretest-posttest design

#6 MH cluster sample

#7 TI (randomised OR randomized)

#8 AB random*

#9 TI trial

#10 MH (sample size) AND AB (assigned OR allocated OR control)

#11 MH placebos

#12 PT randomized controlled trial

#13 AB control W5 group

#14 MH (crossover design) OR MH (comparative studies)

#15 AB cluster W3 RCT

#16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR#10 OR #11 OR #12 OR #13 OR #14 OR #15

NB: the filter also includes additional terms to exclude animals studies, which were omitted on this occasion.

Appendix 2

The Joanna Briggs Institute Critical Appraisal Checklist for Randomized Controlled Trials

Q1 Was true randomization used for assignment of participants to treatment groups? Yes, No, Unclear, NA

Q2 Was allocation to treatment groups concealed? Yes, No, Unclear, NA

Q3 Were treatment groups similar at the baseline? Yes, No, Unclear, NA

Q4 Were participants blind to treatment assignment? Yes, No, Unclear, NA

Q5 Were those delivering treatment blind to treatment assignment? Yes, No, Unclear, NA

Q6 Were outcomes assessors blind to treatment assignment? Yes, No, Unclear, NA

Q7 Were treatment groups treated identically other than the intervention of interest? Yes, No, Unclear, NA

Q8 Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? Yes, No, Unclear, NA

Q9 Were participants analyzed in the groups to which they were randomized? Yes, No, Unclear, NA

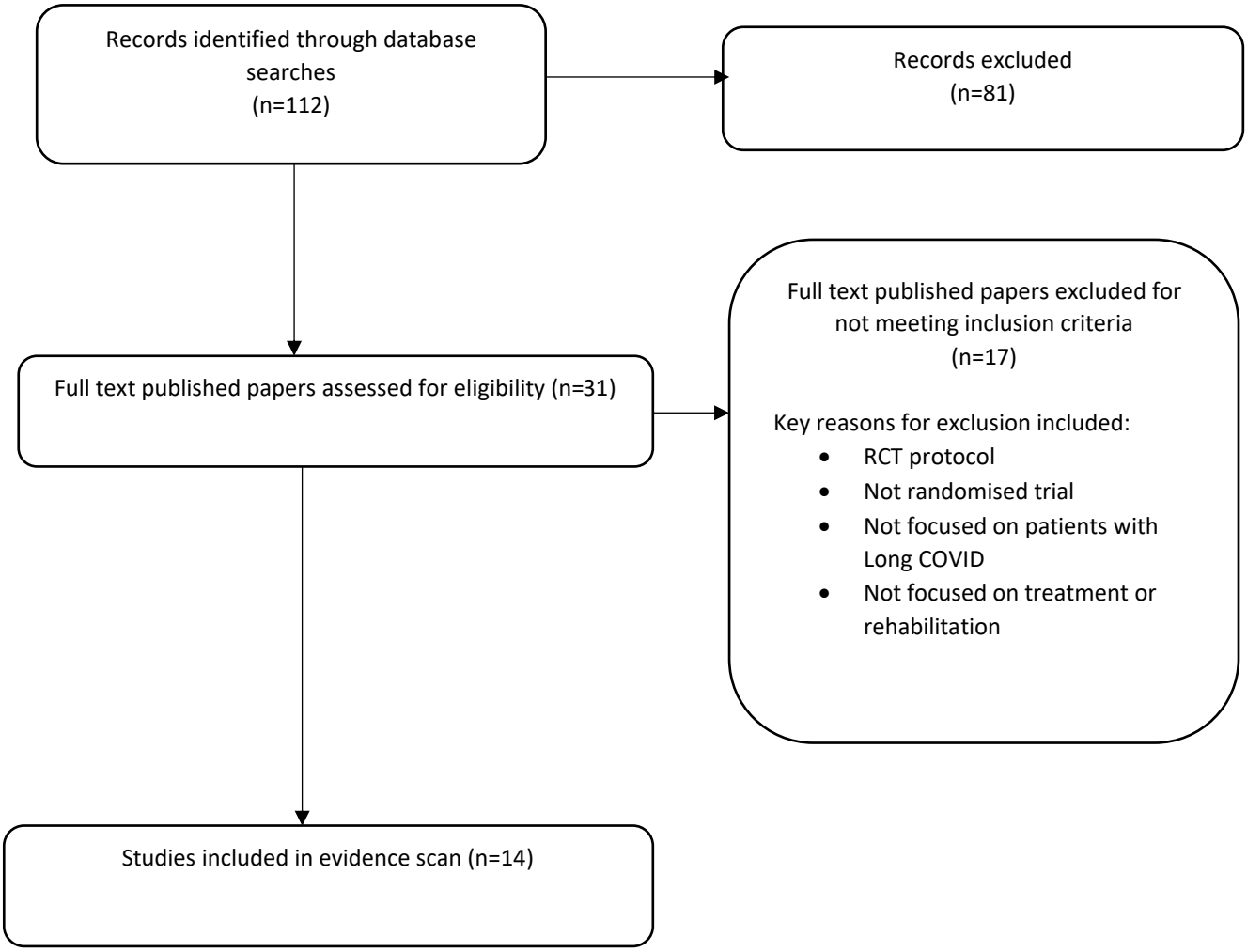
Q10 Were outcomes measured in the same way for treatment groups? Yes, No, Unclear, NA

Q11 Were outcomes measured in a reliable way? Yes, No, Unclear, NA

Q12 Was appropriate statistical analysis used? Yes, No, Unclear, NA

Q13 Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial? Yes, No, Unclear, NA.

Appendix 3: Flow of studies through the review



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CRD (Centre for Reviews and Dissemination), University of York;
and the London School of Hygiene and Tropical Medicine.

The NIHR Policy Research Programme Reviews Facility collaboration has grown out of a previous 'reviews facility' in Health Promotion and Public Health based at the EPPI Centre, and has been funded by the Department of Health and Social Care since 1995.

First produced in 2022 by:

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