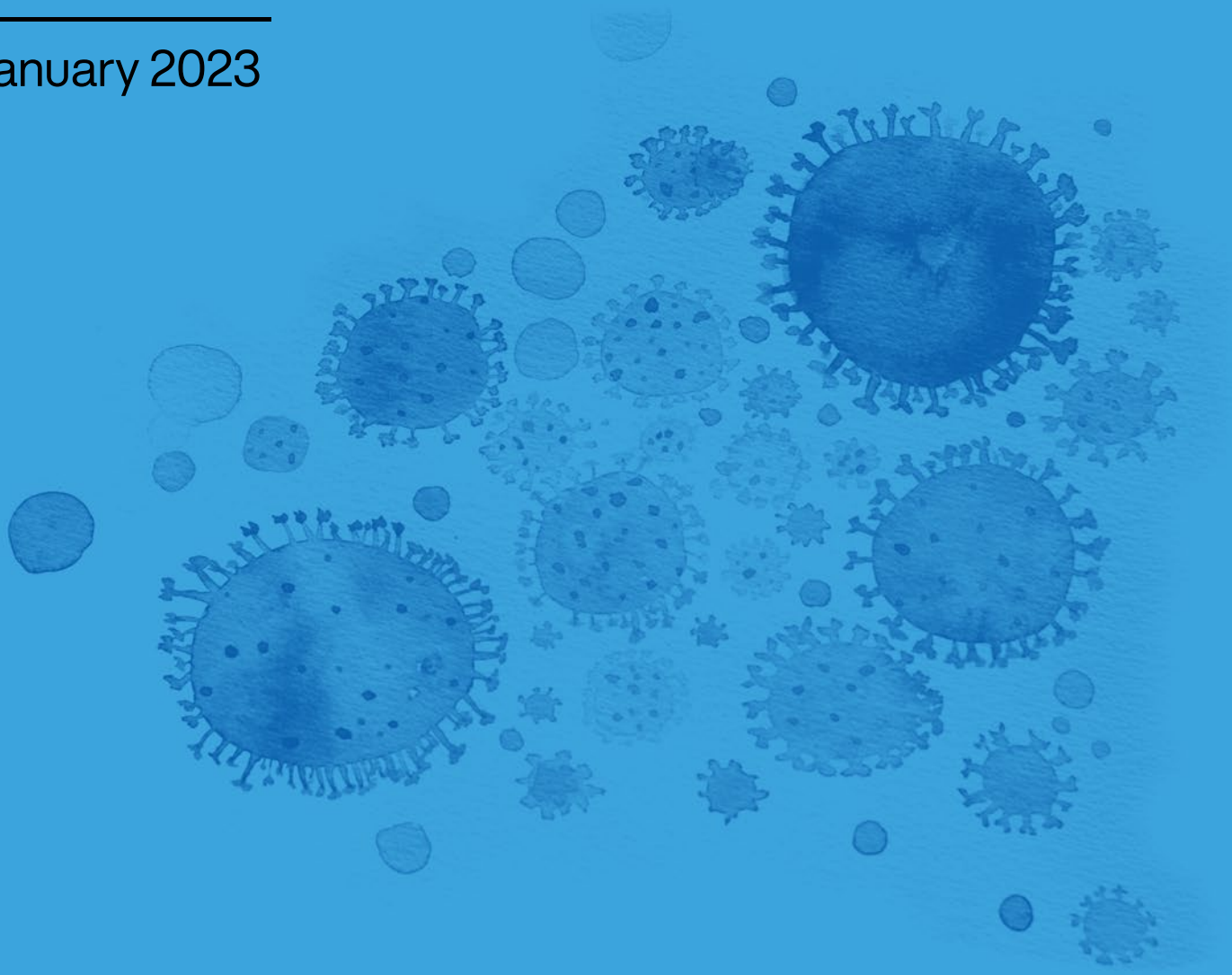
NIHR Policy Research Programme Reviews Facility

To support national policy development and implementation

Treatment and rehabilitation of Long COVID

A scope of the literature: update

January 2023



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Treatment and rehabilitation of Long COVID: A scope of the literature. Update January 2023

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Summary

- We identified 12 randomised controlled trials published since September 2022 that were focused on Long COVID treatment or rehabilitation. Across our three reports produced to date, we have identified and assessed 37 trials published between January and December 2022.
- Half of the trials included in this update had a primary focus on treating persistent problems with respiratory function and physical fitness (n=6). Other trials focused on olfactory dysfunction (n=2); and cognitive problems and long-term fatigue (n=1). Three trials evaluated non-specific interventions for treating Long COVID symptoms (n=3).
- Seven trials were rated positively for at least 11 out of the 13 criteria that we assessed.

Introduction

This is the third report 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 randomised controlled trials (RCTs) evaluating treatment or rehabilitation for Long COVID published in the three-month period between September and December 2022.

Method

Identification of studies

We searched the Cochrane Central Register of Controlled Trials (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-19 infection. Searches of MEDLINE, Embase, PsycINFO and CINAHL were also conducted to identify any trials that had not been incorporated into CENTRAL. We translated the CENTRAL search strategy for use in each database and used study design search filters to restrict retrieval to randomised controlled trials.

Searches were limited to studies added to the databases or published in 2022, and no language restrictions were applied. Due to the rapid nature of the project, the database searches were designed to balance the need to retrieve as many relevant trials as possible against the limited time available for screening. Records were downloaded into EndNote and deduplicated against the search results from previous updates. Full search strategies for CENTRAL, MEDLINE, Embase, PsycINFO and CINAHL can be found in Appendix 1 (page 13).

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. Interventions that had a primary focus on general rehabilitation from COVID-19 following hospitalisation or severe infection were excluded.

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.[1]

Publication type and status - any publication type, except pre-prints and conference abstracts, which report findings from a RCT (e.g. full papers, research letters, brief reports etc).

Quality assessment

Each study was appraised according to the Joanna Briggs Institute (JBI) Checklist for Randomized Controlled Trials.[2] In contrast to the Cochrane Risk of Bias Tool,[3] 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 outcome data. 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 21).

Key findings

For this update, we screened 401 records and identified 12 RCTs that had been published since September 2022.[4-15] We identified and assessed a similar number of RCTs in our previous update (n=11), which covered the period between July to September 2022[1]. The flow of studies through the current update is shown in Appendix 3 (page 22). Table 1 (page 5) presents the aim(s) and key characteristics of the 12 trials.

Interventions

Six of the 12 trials in the current update had a primary focus on people with persistent problems with their respiratory health and physical fitness.[5-9, 12] Three of these six trials evaluated physical therapy-based interventions – a manual diaphragm release technique combined with inspiratory muscle training;[12] a home-based respiratory muscle training programme supervised by telerehabilitation;[8] and Pilates/aqua-Pilates training.[5] Two of the six trials investigated the effectiveness of the drugs Pirfenidone[6] and Treamid,[7] as potential treatments for conditions such as post COVID lung fibrosis and shortness of breath (dyspnoea). The sixth trial examined the effectiveness of infrared low-level laser therapy (photobiomodulation) for improving functional capacity and decreasing fatigue levels.[9]

One trial evaluated the use of an oral supplement containing palmitoylethanolamide/luteolin for individuals with persistent cognitive problems and fatigue after mild COVID-19.[14] Three other trials focused on non-specific interventions for treating Long COVID symptoms.[10, 11, 15] One of these trials evaluated a supervised multicomponent exercise program,[11] whereas the other two focused on oral treatments - high-dose Coenzyme Q10 (CoQ10) capsules [10] and a hemp derived preparation.[15]

Only two trials included in the current update focused primarily on the persistent loss or distortion of the sense of smell (olfactory dysfunction).[4, 13] This contrasts with the findings of our previous

[1] Raine G, Khouja C, Harden M, Sutcliffe K, Sowden A (2022) Treatment and rehabilitation of Long COVID: A scope of the literature. London: Update October 2022. EPPI Centre, UCL Social Research Institute, UCL Institute of Education, University College London.

report (October 2022) in which the majority of evidence focused on olfactory dysfunction (7 out of 11 RCTs).

Participants

Half of the trials recruited participants who had experienced persistent effects for at least four weeks after the onset of COVID symptoms or diagnosis (n=6).[8, 10-14] In four out of these six trials, the individuals who were recruited had experienced ongoing effects for at least 12 weeks.[8, 10, 11, 14] Another trial recruited post COVID patients who had anosmia symptoms for an average of approximately 19 days before starting the intervention.[4]

In two studies, participants were recruited after recovery from COVID, but no further details were reported.[6, 9] In a third, the population comprised recovered patients, 'many' of whom had experienced Post-Acute COVID-19 Syndrome (PASC) for more than six months.[15] Participants were recruited up to four weeks after recovery in another trial,[7] and at least one month after hospital discharge in the remaining trial.[5]

Countries

Three of the 12 trials were conducted in Egypt;[4, 9, 12] and two in Spain.[8, 11] The remaining seven trials were conducted in Denmark;[10] India;[6] Iran;[5] Italy;[14] Netherlands;[13] Russia;[7] and the USA.[15]

Trial quality

Assessments of the trials against the JBI criteria are provided in Table 2 (pages 9 and 10). Two trials were assessed as having a low risk of bias for all 13 appraisal criteria.[8, 13] We rated one trial positively for 12 out of the 13 criteria;[7] and four trials met 11 criteria.[9, 10, 12, 14] In relation to the five studies that met 11 or 12 out of the 13 criteria, we were unable to rate Bazdyrev et al. positively for the use of an Intention to Treat (ITT) analysis (Q9) owing to a lack of clarity about how their modified ITT analysis had been conducted.[7]

We could not tell if a true method of randomisation was used in the trial by Versace et al. (Q1),[14] and it was unclear if an appropriate statistical analysis had been conducted by both Versace et al. and Elbanna et al. (Q12)[9, 14] In the latter trial, it was also not possible to tell if an appropriate procedure was used to prevent the researchers from knowing whether the next patient would be allocated to the treatment or comparator group (allocation concealment) (Q2).[9]

In the trial by Hansen et al., there were significant differences between the intervention and control group at baseline in relation to the severity of post COVID symptoms (Q3), and it was unclear if an ITT analysis had been conducted (Q9).[10] We were also unable to tell if Nagy et al. had conducted an ITT analysis, and the personnel responsible for delivering the intervention were aware of patients' group allocation (Q5).[12]

The remaining five trials gained positive ratings for between four and ten criteria.[4, 5, 6, 11, 15] A number of common issues were identified across these studies. For example, in three of the five studies, there was no blinding of either trial participants or the personnel who administered the treatment (Q4 & Q5).[4, 5, 11] However, in the trials by Bagherzadeh-Rahmani et al. and Jimeno-Almazán et al., the nature of the intervention potentially precluded the blinding of these individuals.[5, 11] In the other two trials, we could not tell if the personnel who administered the treatment were blinded.[6, 15]

It was not possible to tell whether the trial personnel who assessed the outcomes of interest were blinded to participants' group allocation in four of the studies (Q6).[5, 6, 11, 15] In three of the five trials, we could not tell if an ITT analysis was conducted (Q9),[5 ,6, 11] and in a fourth, it had not been used.[15] We also could not tell if an appropriate procedure was used for allocation concealment (Q2) in three of the five trials.[5, 6, 11]

In the study by Young et al.,[15] study participants were blinded up until day 28. It was then discovered that the placebo given to the control group contained therapeutic concentrations of terpenes. A decision was taken to continue the trial despite the lack of a true placebo. At this point, the blinding of participants was ended and both study groups were given the active product for a further period of 28 days.

To conclude, this third evidence scan identified 12 RCTs published between September and December 2022 that examined interventions for the treatment or rehabilitation of people with Long COVID. Across our three reports produced to date, we have now identified and assessed 37 trials published since January 2022. Most of the trials included in the current update had a primary focus on improving respiratory function and physical fitness. Trial quality varied, but seven were rated positively for at least 11 out the 13 criteria that we assessed.

Table 1: Study characteristics (n=12)

First author Country	Aim of study	Main symptom or effect experienced	Post COVID time	Participants' gender (n) and % female	Primary outcome of interest	Comparator
Aref[4] Egypt	To assess the potential role of Ivermectin when administered locally as a nanosuspension nasal spray in the treatment of individuals with post-COVID-19 anosmia	Olfactory dysfunction	After symptom onset or diagnosis: anosmia duration before starting treatment was 19.5 days in the intervention group and 19.1 in the control group	Mixed (96) 25% female (24/96)	Olfactory function	Isotonic saline nasal spray
Bagherzadeh-Rahmani[5] Iran	To investigate the effects of eight-week Pilates and aqua-Pilates training on pulmonary function and quality of life in patients with COVID-19	Respiratory or cardiovascular function or physical fitness: dyspnoea Fatigue/lack of energy	After discharge: at least one month post discharge	Mixed (45) 48 recruited 47% female (21/45)	Pulmonary/respiratory function: forced vital capacity (FVC); forced expiratory volume in the first second (FEV1); FEV1/FVC ratio Quality of life	No training
Banerjee[6] India	To assess the effect of Pirfenidone on spirometry parameters in post recovery COVID 19 patients with diagnosed pulmonary fibrosis	Lung abnormalities: pulmonary fibrosis	Unclear/not reported: post recovery COVID-19 patients	Mixed (70) 27% female (19/70)	Pulmonary/respiratory function: FEV1, FVC, FEV1 /FVC ratio, PEFR	Placebo - no further details given
Bazdyrev[7] Russia	To assess the efficacy of Treamid and its tolerability and safety profile in patients discharged after COVID pneumonia	Lung abnormalities: fibrotic changes in the lungs Respiratory or cardiovascular	After recovery: screening period of up to four weeks, after a negative test	Mixed (60) 56% female (33/59)	Pulmonary/respiratory function: improvement in FVC and/or DLCO (defined as a relative increase in FVC of ≥ 10% or a relative increase in FVC in the range of ≥ 5 to < 10% plus a	Placebo (standard rehabilitation therapy)

		function or physical fitness: decreased lung function; moderate or severe dyspnoea			relative increase in DLCO of ≥ 15%) at week four compared with baseline Feasibility, tolerability and/or safety	
Del Corral[8] Spain	To evaluate the effects of a home-based respiratory muscle training programme supervised by telerehabilitation on health-related quality of life and exercise tolerance in individuals with long-term post-COVID-19 symptoms	Respiratory or cardiovascular function or physical fitness: dyspnoea Fatigue/lack of energy	After symptom onset or diagnosis: at least three months after COVID-19 diagnosis	Mixed (88) 72% female (63/88)	Physical fitness: exercise tolerance Health-related quality of life	Sham treatment (threshold pressure device that lacked resistance)
Elbanna[9] Egypt	To determine the effect of Photobiomodulation (infrared low-level laser therapy) on functional capacity and fatigability in seniors with post-COVID-19 syndrome	Fatigue/lack of energy Decreased ability to perform daily activities	Unclear/not reported: patients who had recently recovered from COVID-19	Mixed (100) Female % not reported	Fatigue Performing daily activities	Sham photobiomodulation (same tool, process etc. with no light)
Hansen[10] Denmark	To investigate whether treating patients with high-dose CoQ10 (coenzyme Q10) can reduce the number and/or severity of post-COVID symptoms	General/multiple symptoms: the most prevalent Long COVID symptoms at baseline were concentration difficulties, mental fatigue, physical fatigue, headache, and muscle weakness	After symptom onset or diagnosis: more than two persisting symptoms 12 weeks after COVID-19. Mean Interval between COVID-19 onset and enrolment = 288.55 days	Mixed (119) 75% female (89/119)	Change in the number and/or severity of PCC related symptoms	Placebo - soy oil capsules

Jimeno-Almazán[11] Spain	To evaluate a tailored exercise program, based on multicomponent exercise training, versus self-management, on the recovery of persistent or recurrent symptoms and functional limitation after COVID-19	General/multiple symptoms: including dyspnoea; fatigue; cognitive impairment; sleep disturbance; low mood; myalgia	After symptom onset or diagnosis: patients presenting with a chronic symptomatic phase, lasting more than 12 weeks from the onset of symptoms. Mean time from diagnosis to study entry was 33 weeks	Mixed (39) 74% female (29/39)	Pulmonary/respiratory function - including FEV1, FVC, FEV1 /FVC ratio; dyspnoea Physical fitness: cardiovascular fitness and muscle strength - including VO2max; rate of perceived exertion; heart rate; bench press; half squat; Sit to Stand; handgrip strength; leg extensions Health related quality of life Psychological: Anxiety; depression Fatigue Performing daily activities Post COVID functional status	A self-management rehabilitation leaflet published by the World Health Organization
Nagy[12] Egypt	To determine whether the addition of manual diaphragm release to an inspiratory muscle training programme is more effective than inspiratory muscle training alone in reducing blood pressure, dyspnoea, fatigue, and aerobic performance capacity in men with post-COVID-19 syndrome	Lung abnormalities: mild to moderate lung fibrosis Respiratory or cardiovascular function or physical fitness: intolerance to physical exercise; hypertension	After symptom onset or diagnosis: four weeks since the first positive COVID-19 test	Male only (60)	Pulmonary/respiratory function: Inspiratory muscle strength	Inspiratory muscle training using the POWERbreath device

Schepens[13] Netherlands	To determine the efficacy of a short oral prednisolone treatment on patients with persistent olfactory disorders after COVID-19	Olfactory dysfunction	After symptom onset or diagnosis: patients with olfactory dysfunction persisting for more than four weeks, within 12 weeks after COVID-19 diagnosis	Mixed (115) 63% female (73/115)	Olfactory function	Placebo in combination with olfactory training
Versace[14] Italy	To investigate the effects of oral palmitoylethanolamide co-ultra-micronised with the flavonoid luteolin (PEA-LUT) in patients with cognitive complaints and fatigue after mild COVID-19	Cognitive function Fatigue/lack of energy	After symptom onset or diagnosis: average time since symptom onset was 291 days for the intervention group and 290 days for placebo group	Mixed (34) 65% female (22/34)	Cognitive: neurophysiological/ brain imaging: intracortical GABAB-ergic neurotransmission indexed with long-interval intracortical inhibition	Placebo- sublingual inert microgranules
Young[15] USA	To measure the efficacy of Formula C, a cannabidiol (CBD)-rich, whole-flower terpene-rich preparation in managing Post-Acute COVID-19 Syndrome (PACS) symptoms	General/multiple symptoms: ongoing symptoms of PACS	Unclear/not reported: patients in the post-acute recovery phase – 'many' had PACS for over 6 months	Mixed (31) (23 completed) 57% female (13/23)	Reduction in patient reported outcomes; change in clinical status	Placebo - organic hempseed oil Later testing revealed that the placebo contained therapeutic levels of terpenes

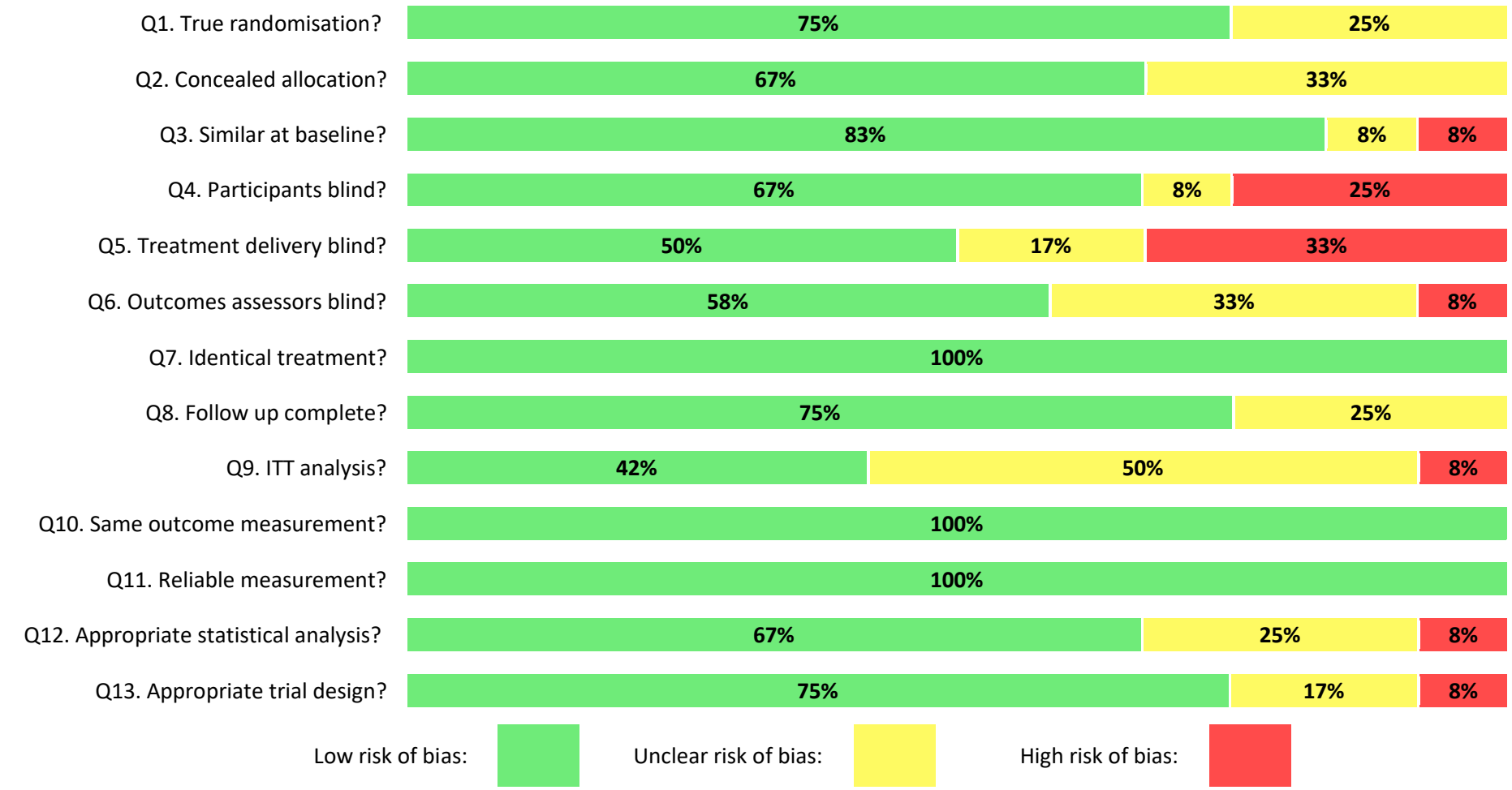
Table 2: JBI risk of bias assessment

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?
Aref (2022)	+	+	+	-	-	-	+	+	+	+	+	+	+
Bagherzadeh-Rahmani (2022)*	?	?	+	-	-	?	+	?	?	+	+	+	?
Banerjee (2022)	?	?	+	?	?	?	+	?	?	+	+	?	?
Bazdyrev (2022)	+	+	+	+	+	+	+	+	?	+	+	+	+
Del Corral (2022)	+	+	+	+	+	+	+	+	+	+	+	+	+
Elbanna (2022)	+	?	+	+	+	+	+	+	+	+	+	?	+
Hansen (2022)	+	+	-	+	+	+	+	+	?	+	+	+	+
Jimeno-Almazán (2022)	+	?	+	-	-	?	+	?	?	+	+	+	+
Nagy (2022)	+	+	+	+	-	+	+	+	?	+	+	+	+
Schepens (2022)	+	+	+	+	+	+	+	+	+	+	+	+	+
Versace (2022)	?	+	+	+	+	+	+	+	+	+	+	?	+
Young (2022)	+	+	?	+**	?	?	+	+	-	+	+	-	-

* Study was described in the paper as both a randomised controlled trial and a quasi-experimental study.

** Blinding was only maintained for 28 days after which both the intervention and placebo groups were given the same active drug.

+ = low risk of bias; - = high risk of bias; and ? = unclear risk of bias



NB: figures may not add up to 100% due to rounding.

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Appendix 1 – search strategies

Cochrane Controlled Register of Trials (CENTRAL)
via Wiley http://onlinelibrary.wiley.com/
Issue: Issue 11 of 12, November 2022
Date searched: 7th December 2022
Records retrieved: 758
Although 758 records were identified overall in CENTRAL, trial register records were removed from this set, leaving a total of 593 records downloaded for this update.

#1 MeSH descriptor: [COVID-19] this term only and with qualifier(s): [complications - CO] 120
#2 MeSH descriptor: [COVID-19] this term only 2553
#3 MeSH descriptor: [SARS-CoV-2] this term only 1187
#4 MeSH descriptor: [Syndrome] this term only 5641
#5 MeSH descriptor: [Survivors] this term only 1292
#6 #2 or #3 2558
#7 #4 or #5 6932
#8 #6 and #7 24
#9 #1 or #8 144
#10 (long next (covid* or covid-19 or covid19 or coronavirus) or longcovid*):ti,ab,kw 162
#11 (post next (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) or postcovid*):ti,ab,kw 392
#12 ((post acute or postacute) near/2 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 735
#13 PASC:ti,ab,kw 31
#14 (sequela* near/6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 92
#15 (chronic near/2 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 24
#16 (ongoing next (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 81
#17 ((long* term or longterm) near/3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 486
#18 (persist* near/6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 153
#19 ((post discharg* or postdischarg*) near/4 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 651
#20 ((long haul* or longhaul*) near/6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 298
#21 (surviv* near/3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 146
#22 (after next (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 190
#23 ((ongoing or lasting or prolonged or fluctuat* or residual* or continu* or linger*) near/6 (symptom* or effect* or complication* or sequela* or syndrome or illness* or disorder$ or dysfunction* or impair* or impact* or consequence*) near/6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 103
#24 {OR #10-#23} 1737
#25 #9 or #24 with Cochrane Library publication date Between Jan 2022 and Dec 2022, in Trials 750
#26 #9 or #24 with Publication Year from 2022 to 2022, in Trials 636
#27 #25 or #26 758

MEDLINE ALL
(includes: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE)
via Ovid http://ovidsp.ovid.com/
Date range: 1946 to December 06, 2022
Date searched: 7th December 2022
Records retrieved: 435

The MEDLINE strategy below includes a search filter to limit retrieval to RCTs using the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity and precision-maximizing version (2008 revision); Ovid format.

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from: www.training.cochrane.org/handbook.

1 post-acute COVID-19 syndrome.mp. (1522)
2 COVID-19 post-intensive care syndrome.mp. (5)
3 COVID-19/co [Complications] (12587)
4 COVID-19/ or SARS-CoV-2/ (204178)
5 Syndrome/ (121689)
6 Survivors/ (29496)
7 5 or 6 (151071)
8 4 and 7 (858)
9 1 or 2 or 3 or 8 (13474)
10 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,kf,ot,bt. (2252)
11 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,kf,ot,bt. (5981)
12 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (549)
13 PASC.ti,ab,kf,ot,bt. (494)
14 (sequela$ adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (1718)
15 (chronic adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (247)
16 (ongoing adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (2851)
17 ((long$ term or longterm) adj3 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (1569)
18 (persist$ adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (2881)
19 ((post discharg$ or postdischarg$) adj4 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (70)
20 ((long haul$ or longhaul$) adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (199)
21 (surviv$ adj3 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (2338)
22 (after adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (6452)

23 ((ongoing or lasting or prolonged or fluctuat$ or residual$ or continu$ or linger$) adj6 (symptom$ or effect$ or complication$ or sequela$ or syndrome or illness$ or disorder$ or dysfunction$ or impair$ or impact$ or consequence$) adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (2063)
24 or/10-23 (22988)
25 9 or 24 (33084)
26 randomized controlled trial.pt. (582495)
27 controlled clinical trial.pt. (95121)
28 randomi#ed.ab. (698698)
29 placebo.ab. (233853)
30 clinical trials as topic.sh. (200646)
31 randomly.ab. (397083)
32 trial.ti. (275254)
33 26 or 27 or 28 or 29 or 30 or 31 or 32 (1533758)
34 exp animals/ not humans.sh. (5072762)
35 33 not 34 (1413290)
36 25 and 35 (948)
37 limit 36 to yr="2022 -Current" (428)
38 2022*.dt. (1494848)
39 36 and 38 (391)
40 37 or 39 (435)

Embase
via Ovid http://ovidsp.ovid.com/
Date range: 1974 to 2022 December 06
Date searched: 7th December 2022
Records retrieved: 748

The Embase strategy below includes a search filter to limit retrieval to RCTs:

Lefebvre C, Eisinga A, McDonald S, Paul N. Enhancing access to reports of clinical trials published world-wide - the contribution of EMBASE records to the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library. Emerg Themes Epidemiol 2008;5:13

1 long COVID/ (2795)
2 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,kw,ot. (2215)
3 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,kw,ot. (7460)
4 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (515)
5 PASC.ti,ab,kw,ot. (598)
6 (sequela$ adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (2100)
7 (chronic adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (290)
8 (ongoing adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (2851)
9 ((long$ term or longterm) adj3 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (1838)
10 (persist$ adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (3514)

11 ((post discharg$ or postdischarg$) adj4 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (119)
12 ((long haul$ or longhaul$) adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (214)
13 (surviv$ adj3 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (3262)
14 (after adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (8325)
15 ((ongoing or lasting or prolonged or fluctuat$ or residual$ or continu$ or linger$) adj6 (symptom$ or effect$ or complication$ or sequela$ or syndrome or illness$ or disorder$ or dysfunction$ or impair$ or impact$ or consequence$) adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (2445)
16 or/2-15 (27798)
17 1 or 16 (28079)
18 random$.ti,ab. (1864887)
19 factorial$.ti,ab. (45346)
20 crossover$.ti,ab. (86944)
21 cross-over$.ti,ab. (36440)
22 placebo$.ti,ab. (352502)
23 (doubl$ adj blind$).ti,ab. (236309)
24 (singl$ adj blind$).ti,ab. (30022)
25 assign$.ti,ab. (467307)
26 allocat$.ti,ab. (190493)
27 volunteer$.ti,ab. (286001)
28 Crossover Procedure/ (72275)
29 double blind procedure/ (201419)
30 Randomized Controlled Trial/ (740116)
31 single blind procedure/ (48522)
32 controlled clinical trial/ (467687)
33 or/18-32 (2914981)
34 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (6595915)
35 33 not 34 (2600627)
36 17 and 35 (1683)
37 limit 36 to yr="2022 -Current" (892)
38 2022$.dd. (758033)
39 36 and 38 (414)
40 37 or 39 (983)
41 (conference abstract or "conference review").pt. (4629503)
42 40 not 41 (748)

PsycINFO
via Ovid http://ovidsp.ovid.com/
Date range: 1806 to November Week 4 2022
Date searched: 7th December 2022
Records retrieved: 131

The PsycINFO strategy below includes a search filter to limit retrieval to RCTs developed by the information specialist at the Cochrane Common Mental Disorders Group.

1 covid-19/ (14751)
2 coronavirus/ (4953)
3 syndromes/ (16912)
4 sequelae/ (3874)
5 1 or 2 (16929)
6 3 or 4 (20722)
7 5 and 6 (211)
8 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,id,ot. (97)
9 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,id,ot. (448)
10 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (19)
11 PASC.ti,ab,id,ot. (25)
12 (sequela$ adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (123)
13 (chronic adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (13)
14 (ongoing adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (241)
15 ((long$ term or longterm) adj3 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (111)
16 (persist$ adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (134)
17 ((post discharg$ or postdischarg$) adj4 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (7)
18 ((long haul$ or longhaul$) adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (11)
19 (surviv$ adj3 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (168)
20 (after adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (302)
21 ((ongoing or lasting or prolonged or fluctuat$ or residual$ or continu$ or linger$) adj6 (symptom$ or effect$ or complication$ or sequela$ or syndrome or illness$ or disorder$ or dysfunction$ or impair$ or impact$ or consequence$) adj6 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (182)
22 or/8-21 (1529)
23 randomized clinical trials/ (403)
24 randomized controlled trials/ (931)
25 clinical trials/ (12125)
26 clinical trial.md. (35367)
27 (randomi#ed or randomi#ation or randomi#ing).ti,ab,id. (103939)
28 randomly.ti,ab,id. (81469)
29 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster* or control* or crossover or cross over or pragmatic or quasi or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or recruit* or split or substitut* or treat*))).ti,ab,id. (123300)
30 (groups or (control* adj3 group*)).ab. (594365)
31 ((control* or trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw. (18025)
32 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id. (28617)
33 trial.ti. (36477)

34 (placebo or sham).ti,ab,id,hw. (57064)
35 treatment outcome.md. (23003)
36 treatment effectiveness evaluation/ (27259)
37 mental health program evaluation/ (2301)
38 or/23-37 (786756)
39 7 or 22 (1646)
40 38 and 39 (209)
41 limit 40 to yr="2022 -Current" (100)
42 2022$.up. (173169)
43 40 and 42 (125)
44 41 or 43 (131)

CINAHL Plus
via Ebsco https://www.ebsco.com/
Date range: Inception to 20221207
Date searched: 7th December 2022
Records retrieved: 334

The CINAHL strategy below includes a search filter to limit retrieval to RCTs developed by Glanville et al.: Glanville J, Dooley G, Wisniewski S, Foxlee R, Noel-Storr A. Development of a search filter to identify reports of controlled clinical trials within CINAHL Plus. Health Info Libr J 2019;36:73-90.

S1	(MH "Post-Acute COVID-19 Syndrome")	528
S2	TI (long N1 (covid* or covid-19 or covid19 or coronavirus) or longcovid*) OR AB (long N1 (covid* or covid-19 or covid19 or coronavirus) or longcovid*)	885
S3	TI (post N1 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) or postcovid*) OR AB (post N1 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) or postcovid*)	1,166
S4	TI (("post acute" or post-acute or postacute) N3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) OR AB (("post acute" or post-acute or postacute) N3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2))	238
S5	TI PASC OR AB PASC	79
S6	TI (sequela* N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) OR AB (sequela* N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2))	436
S7	TI (chronic N2 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) OR AB (chronic N2 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2))	217
S8	TI (ongoing N1 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) OR AB (ongoing N1 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2))	645
S9	TI ((long* N1 term or long-term or longterm) N3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) OR AB (	819

	(long* N1 term or long-term or longterm) N3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2))	
S10	TI (persist* N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) OR AB (persist* N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2))	723
S11	TI ((post N1 discharg* or post-discharg* or postdischarg*) N4 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) OR AB ((post N1 discharg* or post-discharg* or postdischarg*) N4 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2))	40
S12	TI ((long N1 haul* or long-haul* or longhaul*) N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) OR AB ((long N1 haul* or long-haul* or longhaul*) N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2))	84
S13	TI (surviv* N3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) OR AB (surviv* N3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2))	876
S14	TI (after N1 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) OR AB (after N1 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2))	3,202
S15	TI ((ongoing or lasting or prolonged or fluctuat* or residual* or continu* or linger*) N6 (symptom* or effect* or complication* or sequela* or syndrome or illness* or disorder$ or dysfunction* or impair* or impact* or consequence*) N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) OR AB ((ongoing or lasting or prolonged or fluctuat* or residual* or continu* or linger*) N6 (symptom* or effect* or complication* or sequela* or syndrome or illness* or disorder$ or dysfunction* or impair* or impact* or consequence*) N6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2))	738
S16	(MH "Randomized Controlled Trials")	135,542
S17	(MH "Double-Blind Studies")	53,952
S18	(MH "Single-Blind Studies")	15,844
S19	(MH "Random Assignment")	76,883
S20	(MH "Pretest-Posttest Design")	51,247
S21	(MH "Cluster Sample")	5,134
S22	TI randomised OR randomized	134,345
S23	AB random*	389,543
S24	TI trial	173,256
S25	MH (sample size) AND AB (assigned OR allocated OR control)	4,415
S26	MH (placebos)	13,887

S27	PT (randomized controlled trial)	148,812
S28	AB (control W5 group)	140,423
S29	MH (crossover design) OR MH (comparative studies)	472,527
S30	AB (cluster W3 RCT)	475
S31	MH animals+	105,269
S32	MH (animal studies)	150,370
S33	TI (animal model*)	3,684
S34	S31 OR S32 OR S33	246,753
S35	MH (human)	2,632,347
S36	S34 NOT S35	212,904
S37	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30	994,081
S38	S37 NOT S36	947,110
S39	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	8,286
S40	S38 AND S39	656
S41	S38 AND S39 Limiters - Published Date: 20220101-20221231	314
S42	(ZD 2022*)	355,924
S43	S40 AND S42	279
S44	S41 OR S43	334

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

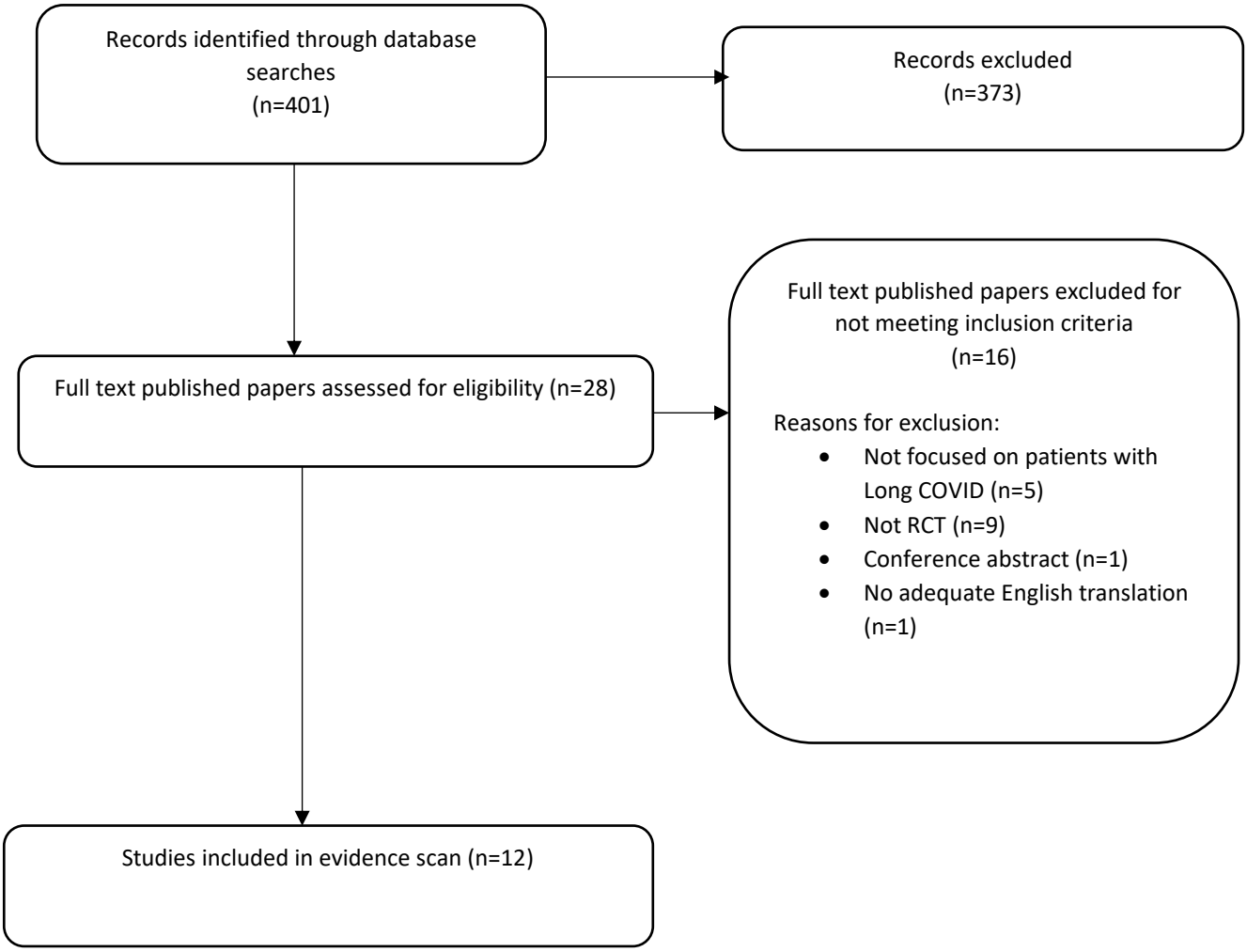
Q10 Were outcomes measured in the same way for treatment groups? Yes, No, Unclear, NA

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



The NIHR Policy Research Programme Reviews Facility aims to put the evidence into development and implementation of health policy through:

- Undertaking policy-relevant systematic reviews of health and social care research
- Developing capacity for undertaking and using reviews
- Producing new and improved methods for undertaking reviews
- Promoting global awareness and use of systematic reviews in decision-making

The Reviews Facility is a collaboration between the following centres:
EPPI Centre (Evidence for Policy and Practice Information Centre),
UCL Institute of Education, University College London;
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.

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UCL Institute of Education, University College London
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