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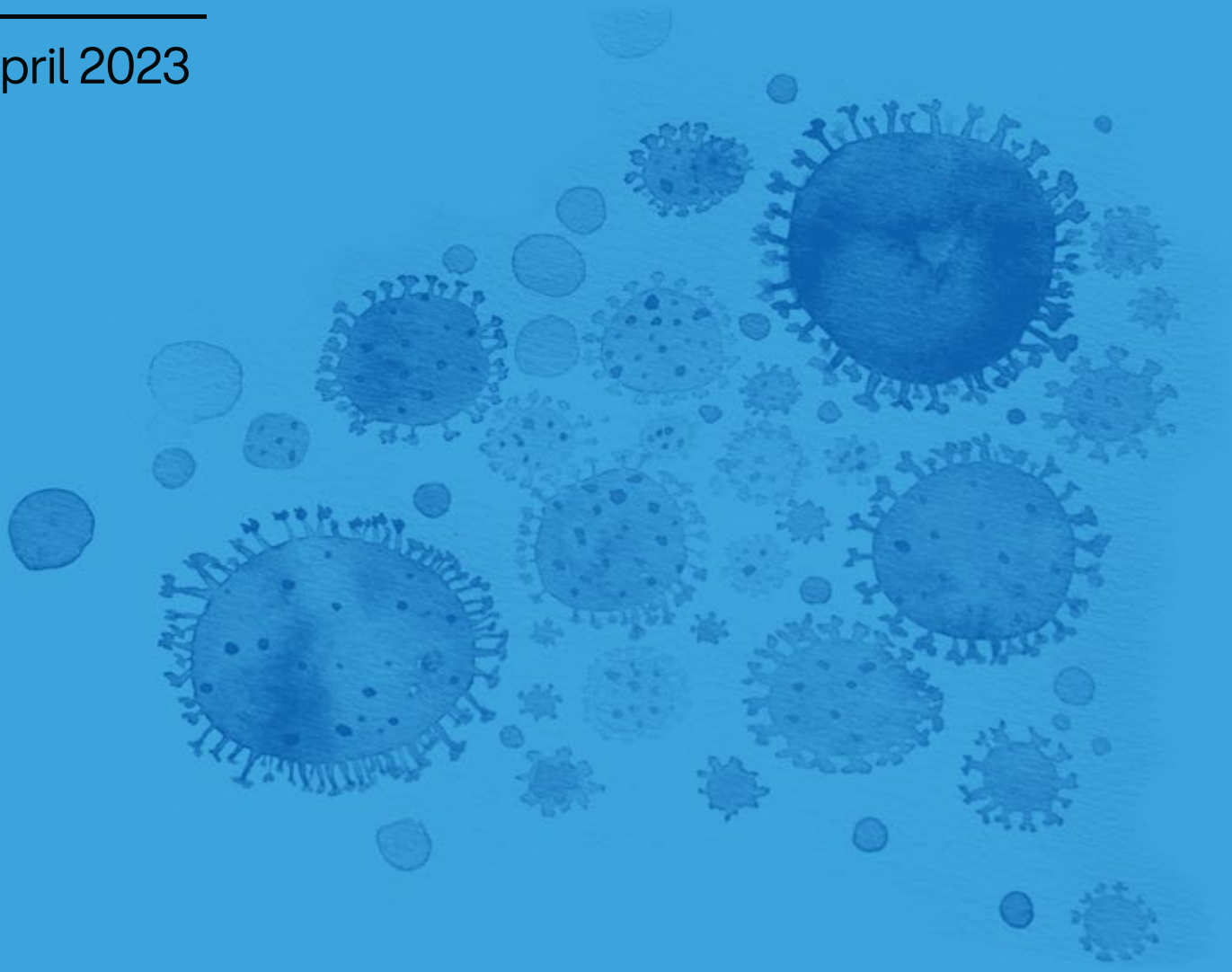
NIHR Policy Research Programme Reviews Facility

To support national policy development and implementation

Treatment and rehabilitation of Long COVID

A scope of the literature: update

April 2023



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

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Summary

- We identified 18 randomised controlled trials published since December 2022 that were focused on Long COVID treatment or rehabilitation. Across our four reports produced to date, we have identified and assessed 55 trials published between January 2022 and March 2023.
- A third 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=5); long-term fatigue (n=2); headaches (n=1) and cognitive impairment, physical and mental fatigue and neuropsychiatric issues (n=1). Three trials evaluated interventions for treating non-specific Long COVID symptoms, all of which were focused on improving physical fitness.
- Five trials were rated positively for at least 11 out of the 13 criteria that we assessed. Four trials met 10 criteria and nine gained a positive rating for between five and nine criteria.

Introduction

This is the fourth 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 December 2022 and March 2023.

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.

The search strategies for CENTRAL and MEDLINE were updated to include the new MeSH heading for Long COVID "Post-Acute COVID-19 Syndrome" introduced in 2023. Searches were limited to studies added to the databases or published in 2022 or 2023, 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 can be found in Appendix 1 (page 16).

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 24).

Key findings

We screened 372 records and identified 18 RCTs that had been published since December 2022. [4-21] This is a larger number of trials than we included in our previous three reports in January 2023 (n=12); [22] October 2022 (n=11); [23] and July 2022 (n=14). [24] The flow of studies through the current update is shown in Appendix 3 (page 25). Table 1 (page 6) presents the aim(s) and key characteristics of the 18 trials.

Interventions

Six of the 18 trials had a primary focus on people with persistent problems with pulmonary/respiratory health and physical fitness. [4, 7, 8, 14, 18, 20] Five of these six trials evaluated physical therapy-based interventions – active cycle breathing; [4] low-to moderate-intensity aerobic exercise training; [7] inspiratory muscle training; [14, 18] and home-based pulmonary rehabilitation. [20] One of the six trials investigated the effectiveness of the drug Nebivolol (selective β1 adrenoceptor antagonist) for treating persistent shortness of breath (dyspnoea). [8] The primary outcome in the trial reported by Corna et al. was intervention feasibility which included eligibility rate, recruitment rate, number of dropouts, adverse events, and adherence. The effectiveness of the intervention for improving physical fitness was reported as secondary outcomes. [7]

Five trials focused on the persistent loss or distortion of the sense of smell (olfactory dysfunction) and investigated the effectiveness of various potential treatments - olfactory training; [6, 11] topical steroids and antihistamines; [12] fast-dissolving insulin films; [13] and platelet-rich plasma. [21]

Three trials[1] examined exercise-based rehabilitation programs for non-specific Long COVID symptoms, [10, 15, 16] two of which focused on telerehabilitation. [15, 16] Two other trials focused on treatments for ongoing fatigue, one evaluated the use of L-Arginine plus Vitamin C supplementation [19] and the other examined non-invasive brain stimulation. [17] Another trial assessed the effect of vagus nerve stimulation on persistent headaches. [5] The last trial evaluated a mindfulness-based neuro-meditation programme to treat cognitive impairment, fatigue and neuropsychiatric issues such as sleep disorders, anxiety and depression. [9]

Eight of the 18 RCTs in the current update evaluated interventions incorporating an exercise component and/or breathing training. [4, 7, 10, 14-16, 18, 20] This is a larger proportion than in the two previous updates in January 2023 (4 out of 12 RCTs), [22] and October 2022 (1 out of 11 RCTs). [23] It is similar to the proportion of trials focused on physical therapy and/or breathing training that we included in our first report in July 2022 (6 out of 14 RCTs). [24] The proportion of included trials in the current update that focused on the treatment of olfactory dysfunction is the second largest across our four reports to date (5 out of 18 RCTs). Notably, a recently published core outcome set for Long COVID in adults did not include taste or smell related functioning. [25]

Participants

Ten trials recruited participants who had experienced persistent effects for at least four weeks after the onset of COVID symptoms or diagnosis. [5-7, 9-11, 15, 16, 20, 21] In half of these 10 trials, the individuals who were recruited had experienced ongoing effects for at least 12 weeks after symptom onset or diagnosis (n=5). [5, 10, 11, 20, 21]

In five other trials, participants had experienced ongoing effects for at least four weeks, [19] eight weeks, [13] or 12 weeks, [8, 14, 17] after recovery or hospital discharge. One trial recruited recently recovered COVID patients who had hyposmia or anosmia symptoms for an average of three to four days after testing negative. [12] Another trial recruited individuals who had experienced ongoing pulmonary problems for an average of 1.5 months, but it was unclear whether this referred to time after symptom onset/diagnosis or recovery/discharge. [18] In the remaining trial, the population comprised individuals with symptoms of 'post-COVID' but no time related details were reported. [4]

Countries

Out of the 18 included trials, four were conducted in Egypt; [4, 5, 12, 13] three in Italy; [7, 8, 19] and three in Spain; [10, 14, 15] Two trials were conducted in France [9, 20] Turkey; [16, 18] and the USA. [11, 21] One trial was conducted in Brazil; [17] and Canada. [6]

Trial quality

Assessments of the trials against the JBI criteria are provided in Table 2 (page 11). One trial was assessed as having a low risk of bias for all 13 appraisal criteria. [17] We rated four trials positively for 11 out of the 13 criteria. [7, 12, 14, 18] In two of these four studies, there was no blinding of either trial participants or the personnel who administered the treatment (Q4 & Q5). [7, 14] However, the nature of the interventions potentially precluded the use of blinding as one evaluated an exercise-based

[1] The paper by Jimeno-Almazán et al. was based on the same trial as the one below which we included in our January 2023 update. The paper included in the current update appears to be the full trial report.

Jimeno-Almazán A, Franco-López F, Buendía-Romero Á, et al. Rehabilitation for post-COVID-19 condition through a supervised exercise intervention: a randomized controlled trial. Scandinavian Journal of Medicine & Science in Sports. 2022:1791-801.

programme [7] and the other inspiratory muscle training. [14] In one of the other two trials meeting 11 criteria, we could not tell if participants were blinded to their group allocation (Q4) and an Intention to Treat (ITT) analysis was not used (Q9). [18] In the fourth trial, an ITT analysis was also not used, and we were unclear if an appropriate statistical analysis had been conducted owing to a lack of detail about the sample size required for the study. [12]

Four trials met 10 out of the 13 criteria [5, 6, 11, 15] and nine others were rated positively for between five and nine criteria. [4, 8-10, 13, 16, 19-21] A number of common issues were identified across these 13 studies. For example, in 10 of the trials, we could not tell if an appropriate procedure had been used to prevent researchers from knowing whether the next patient would be allocated to the treatment or comparator group (allocation concealment)(Q2). [4, 5, 8-11, 13, 16, 19, 21]

It was unclear whether participants were blinded in seven of the 13 trials (Q4). [4, 5, 9, 10, 13, 15, 16] In six trials, we could not tell if there was blinding of the personnel who administered the treatment (Q5), [4, 5, 9, 10, 13] and/or those who assessed outcomes of interest (Q6). [4, 8-10, 13] In another six trials, there was no blinding of participants, [19, 20] the personnel who administered the treatment; [15, 16, 19] or both the personnel who administered the treatment and outcome assessors. [11, 20, 21] Again, the nature of the intervention in some of these studies, particularly those that evaluated physical therapy-based programmes, could have prevented the use of blinding.

In seven trials, an ITT analysis was not conducted; [6, 10, 13, 15, 16, 20, 21] and in two others we could not tell if it had been used (Q9). [9, 19] It was unclear if an appropriate statistical analysis had been conducted in five studies (Q12). [4, 8-10, 13] We also could not tell if an appropriate method of randomisation had been used for allocating participants to treatment groups in four trials (Q1). [4, 6, 8, 9]

To conclude, this evidence scan identified 18 RCTs published between December 2022 and March 2023 that examined interventions for the treatment or rehabilitation of people with Long COVID. Across our four reports produced to date, we have now identified and assessed 55 trials published since January 2022. Most the trials in the current update had a primary focus on improving respiratory function and physical fitness (n=6) or treating olfactory dysfunction (n=5). Trial quality varied, but five were rated positively for at least 11 out of the 13 criteria and four met 10 criteria. The other nine trials gained positive ratings for between five and nine criteria.

Table 1: Study characteristics (n=18)

First author Country	Aim of study	Main symptom or effect experienced	Post COVID time	Participants' gender (n) and % female	Primary outcome(s) of interest	Comparator
Ali [4] Egypt	To determine how active cycle breathing affects specific pulmonary outcomes in patients having post-COVID syndrome	Respiratory or cardiovascular function or physical fitness: including difficulty in breathing during the activity of daily living, excessive dyspnoea, excessive cough and sputum production, altered sputum colour and/or viscosity	Unclear/not stated	Mixed (60) 52% female (31/60)	Pulmonary/respiratory function: blood gases Physical fitness: Six-minute walk test (6MWT) Fatigue: Fatigue Assessment Scale (FAS)	Traditional physiotherapy programme that included aerobic exercise, muscle strengthening, and respiratory exercise
Awaad [5] Egypt	To investigate the effect of peripheral neuromodulation in the form of vagus nerve stimulation on headache in Post COVID-19 survivors	Neuropsychiatric: Headache	After symptom onset or diagnosis: up to six months after infection identified by a positive test	Mixed (30) 57% female (17/30)	Neurophysiological/brain imaging: headache pain intensity on VAS and disability on Headache Disability Index (HDI)	Sham vagus nerve stimulation and physical therapy
Berube [6] Canada	To compare the effectiveness of olfactory training versus placebo in the treatment of post-COVID-19 olfactory dysfunction	Olfactory dysfunction	After symptom onset or diagnosis: two months or more since positive test	Mixed (50) 66% female (33/50)	Olfactory function: UPSIT-40	Placebo - odourless propylene glycol
Corna [7] Italy	To study the feasibility of low- to moderate-intensity aerobic exercise training, in addition to standard rehabilitation, in patients with the sequelae of interstitial pneumonia due to COVID-19	Respiratory or cardiovascular function or physical fitness: interstitial pneumonia	After symptom onset or diagnosis: Time between 1st positive swab and randomization: 27.9 ± 7.4 days (experimental group); 33.8 ± 11.9 days (control)	Mixed (32) 41% female (13/32)	Feasibility, tolerability and/or safety: eligibility, recruitment, dropouts, adverse events, and adherence	Standard inpatient rehabilitation

Dal Negro [8] Italy	To compare the effect of nebivolol versus placebo in patients who had low capillary blood volume and complained of dyspnoea for several weeks after COVID-19 pneumonia	Respiratory or cardiovascular function or physical fitness: dyspnoea	After discharge: 12 to 16 weeks after hospital discharge	Mixed (8) 63% female (5/8)	Pulmonary/respiratory function: lung diffusion (DL - CO, NO and ratio, Vc and exhaled NO) and dyspnoea score (and duration), blood haemoglobin, BP and heart rate	Placebo
Hausswirth [9] France	To evaluate the influence of a mindfulness-based intervention on cognitive performance in Long COVID patients	Cognitive function: mental fatigue Fatigue/lack of energy Neuropsychiatric: sleep problems, anxiety, depression	After symptom onset or diagnosis: at least four weeks after initial infection	Mixed (34) 74% female (25/34) (plus a healthy control group 10/15 female)	General or multiple symptoms/clinical outcomes: sleep quality, mood, anxiety, depression, physical and mental fatigue, dyspnoea, muscle and joint pain, and headaches Cognitive: choice-response, pattern comparison, Simon, pursuit rotor, and Corsi block tapping	No intervention
Jimeno-Almazán [10] Spain	To determine the effectiveness of physical exercise, respiratory muscle training, and the self-management World Health Organization (WHO) recommendations leaflet on the recovery of physical fitness, quality of life, and symptom status in people with post-COVID-19 conditions	General/multiple symptoms: lack of concentration; memory problems; brain fog; sleep disturbances; myalgia; low mood; headache; anxiety	After symptom onset or diagnosis: patients presenting with a chronic symptomatic phase, lasting more than 12 weeks from the onset of symptoms	Mixed (80) 69% female (55/80)	Physical fitness: cardiovascular fitness and muscle strength including VO2max; bench press; half squat (1RM and MPVALL); handgrip strength	WHO guidelines for post-COVID-19 related illness rehabilitation "Support for Rehabilitation: Self-Management after COVID-19-Related Illness"
Khan [11] USA	To determine the efficacy of bimodal (visual-olfactory) training vs unimodal training and the efficacy of patient-preferred vs physician-	Olfactory dysfunction	After symptom onset or diagnosis: three months duration initially diagnosed	Mixed (275) 86% female (236/275)	Olfactory function: UPSIT score	Four interventions compared, plus control - no intervention

	assigned scents for COVID-19 post-viral olfactory dysfunction		within two weeks of COVID-19 infection			
Mohamad [12] Egypt	To identify the effectiveness of topical steroids and antihistamines in treating post-COVID-19 hyposmia or anosmia	Olfactory dysfunction	After recovery: recently recovered, complaining of hyposmia or anosmia - mean duration from COVID-19 recovery ranged from 3.3 to 3.6 days	Mixed (240; 207 completed) 16% female (39/240)	Olfactory function: Butanol threshold test; and smell discrimination test	Nasal saline spray
Mohamad [13] Egypt	To assess intranasal fast-dissolving insulin films as the treatment of choice for anosmia	Olfactory dysfunction	After recovery: post-viral with anosmia for more than two months	Mixed (48; 40 completed) 60% female (24/40)	Quality of life: HR QoL	Intranasal fast-dissolving film without insulin
Palau [14] Spain	To evaluate the effect of a 12-week home-based inspiratory muscle training programme on maximal functional capacity and quality of life in patients with Long COVID recovering from a SARS-CoV-2 pneumonia requiring hospitalisation	Respiratory or cardiovascular function or physical fitness: reduced functional capacity	After discharge: at least three months since discharge	Mixed (26) 42% female (11/26)	Pulmonary/respiratory function: change in mean peak VO2 on maximal cardiopulmonary exercise testing (CPET; respiratory exchange ratio)	Usual care - maximal inspiratory pressure checked, no physical therapy
Rodriguez-Blanco [15] Spain	To test the efficacy of a fourteen-day telerehabilitation programme of respiratory and strength exercises in people with post-COVID-19 conditions	General/multiple: symptoms for at least 40 days	After symptom onset or diagnosis: more than 40 days since positive test	Mixed (52; 48 completed) 54% female (26/48)	Pulmonary/respiratory function: Multidimensional Dyspnea-12 (MD12) Physical fitness: Six-minute walk test; 30-second sit to stand test; modified Borg Scale (BS)	Relative rest at home (no intervention - activities of daily living, without associated physical efforts)

					Fatigue: Visual Analogue Fatigue scale (VAFS)	
Sahin [16] Turkey	To evaluate whether adding tele-coaching to a home-based pulmonary rehabilitation programme would have any impact on the effectiveness of the programme	General/multiple: persistent symptoms including dyspnoea	After symptom onset or diagnosis: four weeks after onset	Mixed (48; 42 completed) 33% female (14/42)	Physical fitness: Six-minute walk test	Home-based breathing exercises, strength training, and a regular walking programme, without remote coaching
Santana [17] Brazil	To evaluate the efficacy of M1 high-definition transcranial direct current stimulation associated with rehabilitation in post-acute sequelae of COVID-19 patients with fatigue	Fatigue/lack of energy	After recovery: three to 12 months after confirmed infection	Mixed (70) 64% female (45/70)	Fatigue: Modified Fatigue Impact Scale (MFIS)	Sham stimulation, with rehabilitation
Sari [18] Turkey	To investigate the effectiveness of pulmonary exercise with inspiratory muscle training on exercise capacity, peripheral muscle strength, dyspnoea, quality of life, fatigue, physical activity, anxiety and depression in individuals with post-COVID-19	Respiratory or cardiovascular function or physical fitness including dyspnoea, cough and sputum	Post-COVID-19 patients with pulmonary involvement for 1.5 months	Mixed (26; 24 completed) 33% female (8/24)	Physical fitness: Six-minute walk test; Oxygen saturation, heart rate, respiratory rate, dyspnoea, fatigue and 30-second sit to stand test	Breathing exercises and resistance training (without inspiratory muscle training)
Tosato [19] Italy	To assess the effects of a 28-day oral supplementation with L-arginine plus vitamin C on physical performance, muscle strength, endothelial function, fatigue persistence, and systemic L-arginine	Fatigue/lack of energy	After recovery: at least four weeks after a negative test	Mixed (50; 46 completed) 65% female (30/46)	Physical fitness: Six-minute walk test	Placebo

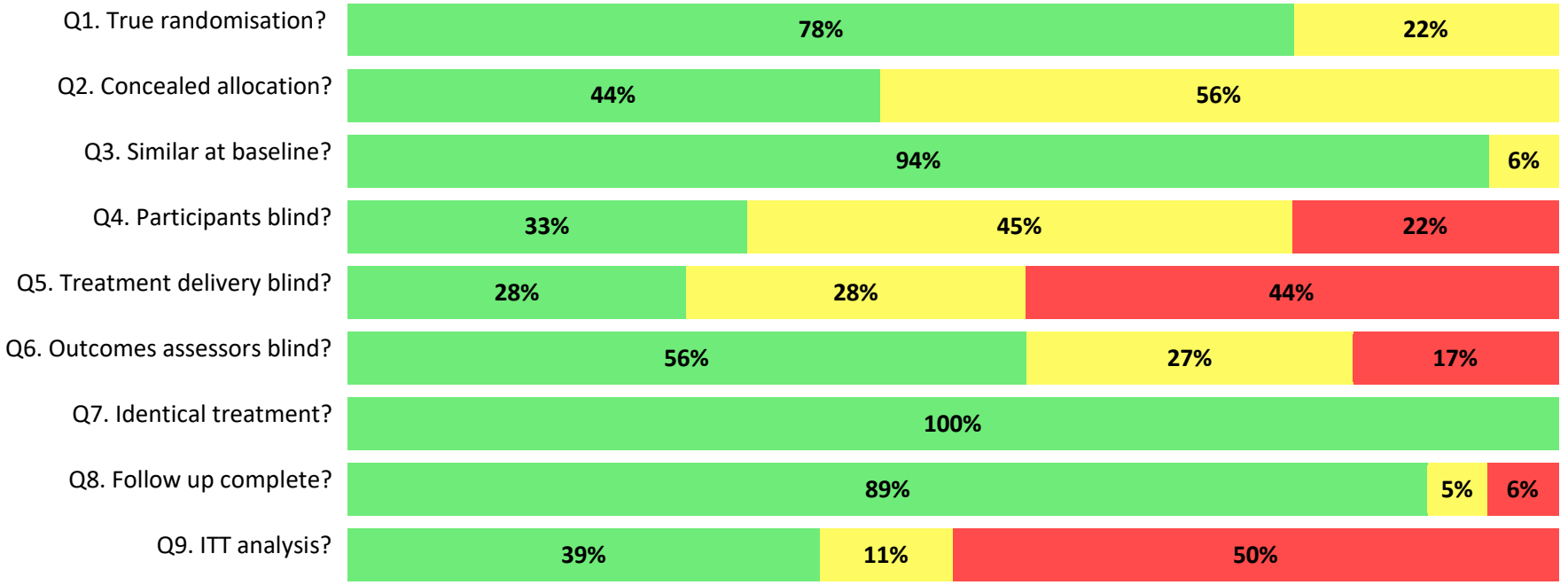
	bioavailability in adults with Long COVID					
Vallier [20] France	To investigate whether home-based rehabilitation would have similar effects compared to inpatient rehabilitation on physical and respiratory variables in post COVID-19 patients	Respiratory or cardiovascular function or physical fitness: at least one physical or respiratory sequela	After symptom onset or diagnosis: mean 141 days since onset	Mixed (22; 17 completed) 29% female (5/17)	Physical fitness: Six-minute walk test	Hospital-based rehabilitation
Yan [21] USA	To evaluate the efficacy and safety of intranasal platelet-rich plasma in a cohort of patients with COVID-19 related persistent olfactory dysfunction	Olfactory dysfunction	After symptom onset or diagnosis: olfactory dysfunction lasting 6 to 12 months after confirmed diagnosis	Mixed (30; 26 completed) 50% female (15/30)	Olfactory function: Sniffin' Sticks - odour threshold, discrimination, and identification (TDI)	Sterile saline intranasal injection

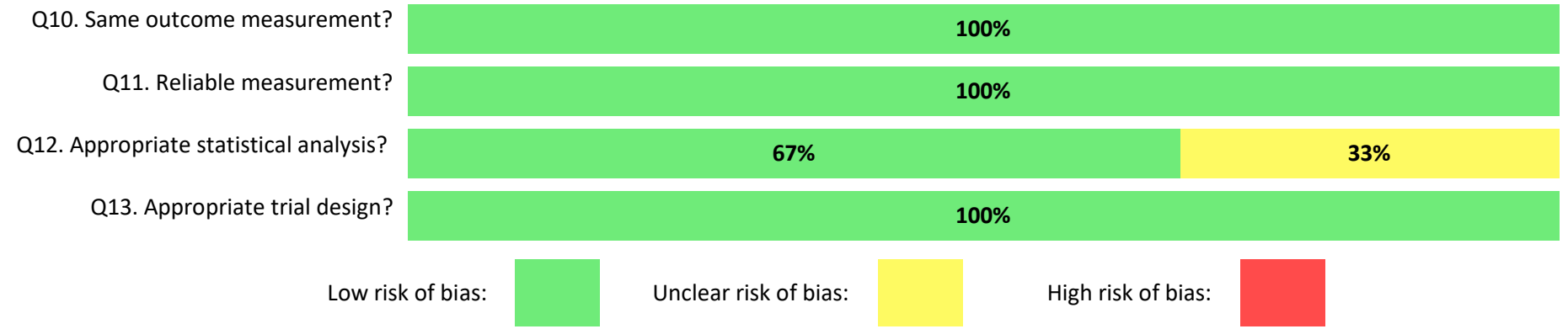
Table 2: JBI risk of bias assessment

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?
Ali (2023)	?	?	+	?	?	?	+	+	+	+	+	?	+
Awaad (2022)	+	?	+	?	?	+	+	+	+	+	+	+	+
Berube (2022)	?	+	+	+	+	+	+	-	-	+	+	+	+
Corna (2022)	+	+	+	-	-	+	+	+	+	+	+	+	+
Dal Negro (2022)	?	?	?	+	+	?	+	+	+	+	+	?	+
Hausswirth (2023)	?	?	+	?	?	?	+	?	?	+	+	?	+
Jimeno-Almazán (2023)	+	?	+	?	?	?	+	+	-	+	+	?	+
Khan (2023)	+	?	+	+	-	-	+	+	+	+	+	+	+
Mohamad (2022)*	+	+	+	+	+	+	+	+	-	+	+	?	+
Mohamad (2022)**	+	?	+	?	?	?	+	+	-	+	+	?	+
Palau (2022)	+	+	+	-	-	+	+	+	+	+	+	+	+
Rodriguez-Blanco (2023)	+	+	+	?	-	+	+	+	-	+	+	+	+

Sahin (2023)	+	?	+	?	-	+	+	+	-	+	+	+	+
Santana (2023)	+	+	+	+	+	+	+	+	+	+	+	+	+
Sari (2022)	+	+	+	?	+	+	+	+	-	+	+	+	+
Tosato (2022)	+	?	+	-	-	+	+	+	?	+	+	+	+
Vallier (2023)	+	+	+	-	-	-	+	+	-	+	+	+	+
Yan (2022)	+	?	+	+	-	-	+	+	-	+	+	+	+

+ = low risk of bias; - = high risk of bias; and ? = unclear risk of bias
* Mohamad et al. [12]; ** Mohamad et al. [13]





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

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22. Raine G, Khouja C, Khatwa M, Sutcliffe K, Sowden A. Treatment and rehabilitation of Long COVID: A scope of the literature. Update January 2023. London: EPPI Centre, UCL Social Research Institute, UCL Institute of Education, University College London; 2023.

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

24. Raine G, Khouja C, Khatwa M, Sutcliffe K, Sowden A. Treatment and rehabilitation of Long COVID: A scope of the literature. London: EPPI Centre, UCL Social Research Institute, UCL Institute of Education, University College London; 2022.

25. Munblit D, Nicholson T, Akrami A, Apfelbacher C, Chen J, De Groote W, et al. A core outcome set for post-COVID-19 condition in adults for use in clinical practice and research: an international Delphi consensus study. Lancet Respir Med. 2022;10(7):715-24.

Appendix 1 – search strategies

Cochrane Controlled Register of Trials (CENTRAL)
via Wiley http://onlinelibrary.wiley.com/
Issue: Issue 2 of 12, February 2023
Date searched: 6th March 2023
Records retrieved: 774

Although 956 records were identified overall in CENTRAL, trial register records were removed from this set, leaving a total of 774 records downloaded for this update.

#1 MeSH descriptor: [Post-Acute COVID-19 Syndrome] this term only 26
#2 MeSH descriptor: [COVID-19] this term only and with qualifier(s): [complications - CO] 196
#3 MeSH descriptor: [COVID-19] this term only 3972
#4 MeSH descriptor: [SARS-CoV-2] this term only 2174
#5 MeSH descriptor: [Syndrome] this term only 5962
#6 MeSH descriptor: [Survivors] this term only 1515
#7 #3 or #4 4187
#8 #5 or #6 7473
#9 #7 and #8 36
#10 #1 or #2 or #9 240
#11 (long next (covid* or covid-19 or covid19 or coronavirus) or longcovid*):ti,ab,kw 202
#12 (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 446
#13 ((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 834
#14 PASC:ti,ab,kw 40
#15 (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 109
#16 (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 27
#17 (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 84
#18 ((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 539
#19 (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 168
#20 ((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 743
#21 ((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 347
#22 (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 156
#23 (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 205
#24 ((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 113
#25 {OR #11-#24} 1912
#26 #10 or #25 with Cochrane Library publication date Between Jan 2022 and Mar 2023, in Trials 945

#27 #10 or #25 with Publication Year from 2022 to 2023, in Trials 835
#28 #26 or #27 956

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 March 03, 2023
Date searched: 6th March 2023
Records retrieved: 560

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/ (1726)
2 COVID-19 post-intensive care syndrome.mp. (5)
3 COVID-19/co [Complications] (13527)
4 COVID-19/ or SARS-CoV-2/ (217602)
5 Syndrome/ (122071)
6 Survivors/ (29869)
7 5 or 6 (151822)
8 4 and 7 (908)
9 1 or 2 or 3 or 8 (14614)
10 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,kf,ot,bt. (2778)
11 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,kf,ot,bt. (6863)
12 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (640)
13 PASC.ti,ab,kf,ot,bt. (561)
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. (1978)
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. (268)
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. (3064)
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. (1735)
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. (3187)
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. (78)
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. (218)

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. (2544)
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. (7215)
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. (2294)
24 or/10-23 (25615)
25 9 or 24 (36419)
26 randomized controlled trial.pt. (588169)
27 controlled clinical trial.pt. (95209)
28 randomi#ed.ab. (710574)
29 placebo.ab. (236303)
30 clinical trials as topic.sh. (200896)
31 randomly.ab. (403299)
32 trial.ti. (280639)
33 26 or 27 or 28 or 29 or 30 or 31 or 32 (1552806)
34 exp animals/ not humans.sh. (5099189)
35 33 not 34 (1431146)
36 25 and 35 (1071)
37 limit 36 to yr="2022 -Current" (552)
38 (2022* or 2023*).dt. (1888443)
39 36 and 38 (515)
40 37 or 39 (560)

Embase
via Ovid http://ovidsp.ovid.com/
Date range: 1974 to 2023 March 03
Date searched: 6th March 2023
Records retrieved: 962

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/ (3613)
2 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,kw,ot. (2877)
3 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,kw,ot. (8963)
4 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (637)
5 PASC.ti,ab,kw,ot. (716)
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. (2557)
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. (354)
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. (3361)

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. (2221)
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. (4229)
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. (145)
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. (247)
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. (3871)
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. (10024)
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. (2937)
16 or/2-15 (33388)
17 1 or 16 (33745)
18 random$.ti,ab. (1936781)
19 factorial$.ti,ab. (46692)
20 crossover$.ti,ab. (89691)
21 cross-over$.ti,ab. (37386)
22 placebo$.ti,ab. (364021)
23 (doubl$ adj blind$).ti,ab. (242976)
24 (singl$ adj blind$).ti,ab. (31295)
25 assign$.ti,ab. (483424)
26 allocat$.ti,ab. (198280)
27 volunteer$.ti,ab. (292292)
28 Crossover Procedure/ (74380)
29 double blind procedure/ (207980)
30 Randomized Controlled Trial/ (773184)
31 single blind procedure/ (50974)
32 controlled clinical trial/ (468711)
33 or/18-32 (3010911)
34 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (6750515)
35 33 not 34 (2688010)
36 17 and 35 (2050)
37 limit 36 to yr="2022 -Current" (1166)
38 (2022$ or 2023$).dd. (883229)
39 36 and 38 (512)
40 37 or 39 (1264)
41 (conference abstract or "conference review").pt. (4705719)
42 40 not 41 (962)

PsycINFO
via Ovid http://ovidsp.ovid.com/
Date range: 1806 to February Week 3 2023
Date searched: 6th March 2023
Records retrieved: 169

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/ (17401)
2 coronavirus/ (5483)
3 syndromes/ (17135)
4 sequelae/ (3906)
5 1 or 2 (19744)
6 3 or 4 (20975)
7 5 and 6 (241)
8 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,id,ot. (126)
9 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,id,ot. (524)
10 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (25)
11 PASC.ti,ab,id,ot. (27)
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. (141)
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. (17)
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. (269)
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. (127)
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. (154)
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. (13)
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. (191)
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. (342)
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. (214)
22 or/8-21 (1749)
23 randomized clinical trials/ (434)
24 randomized controlled trials/ (959)
25 clinical trials/ (12143)
26 clinical trial.md. (36316)
27 (randomi#ed or randomi#ation or randomi#ing).ti,ab,id. (105471)
28 randomly.ti,ab,id. (82239)
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. (124934)
30 (groups or (control* adj3 group*)).ab. (599537)

31 ((control* or trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw. (18308)
32 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id. (28801)
33 trial.ti. (36979)
34 (placebo or sham).ti,ab,id,hw. (57474)
35 treatment outcome.md. (23248)
36 treatment effectiveness evaluation/ (27513)
37 mental health program evaluation/ (2321)
38 or/23-37 (794011)
39 7 or 22 (1875)
40 38 and 39 (247)
41 limit 40 to yr="2022 -Current" (127)
42 (2022$ or 2023$).up. (211054)
43 40 and 42 (163)
44 41 or 43 (169)

CINAHL Ultimate
via Ebsco https://www.ebsco.com/
Date range: Inception to 20230306
Date searched: 6th March 2023
Records retrieved: 417

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") 636
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*) 1,023
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*) 1,340
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)) 270
S5 TI PASC OR AB PASC 89
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)) 489
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)) 234
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)) 681
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 ((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)) 914

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)) 790
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)) 46
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)) 89
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)) 960
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)) 3,539
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)) 807
S16 (MH "Randomized Controlled Trials") 138,061
S17 (MH "Double-Blind Studies") 54,342
S18 (MH "Single-Blind Studies") 16,013
S19 (MH "Random Assignment") 78,609
S20 (MH "Pretest-Posttest Design") 53,103
S21 (MH "Cluster Sample") 5,331
S22 TI randomised OR randomized 138,346
S23 AB random* 395,445
S24 TI trial 178,679
S25 MH (sample size) AND AB (assigned OR allocated OR control) 4,466
S26 MH (placebos) 14,037
S27 PT (randomized controlled trial) 150,333
S28 AB (control W5 group) 142,688
S29 MH (crossover design) OR MH (comparative studies) 477,414
S30 AB (cluster W3 RCT) 491
S31 MH animals+ 105,607
S32 MH (animal studies) 151,943
S33 TI (animal model*) 3,759
S34 S31 OR S32 OR S33 248,660
S35 MH (human) 2,683,936
S36 S34 NOT S35 214,634
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 1,011,918
S38 S37 NOT S36 964,476
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 9,173

S40 S38 AND S39 736
S41 S38 AND S39 Limiters - Published Date: 20220101-20230331 395
S42 (ZD 2022* OR 2023*) 382,797
S43 S40 AND S42 296
S44 S41 OR S43 417

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

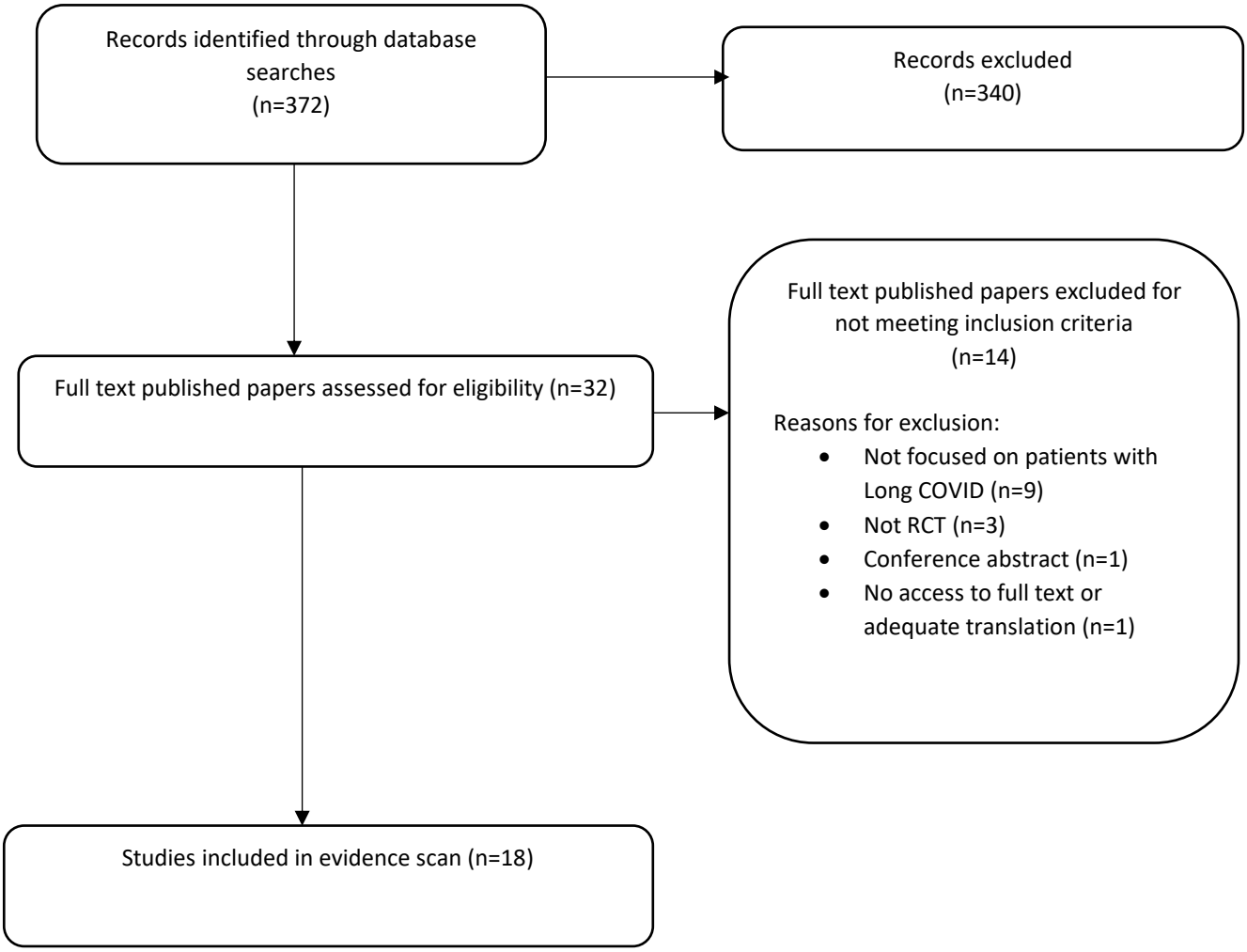
Q10 Were outcomes measured in the same way for treatment groups? Yes, No, Unclear, NA

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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