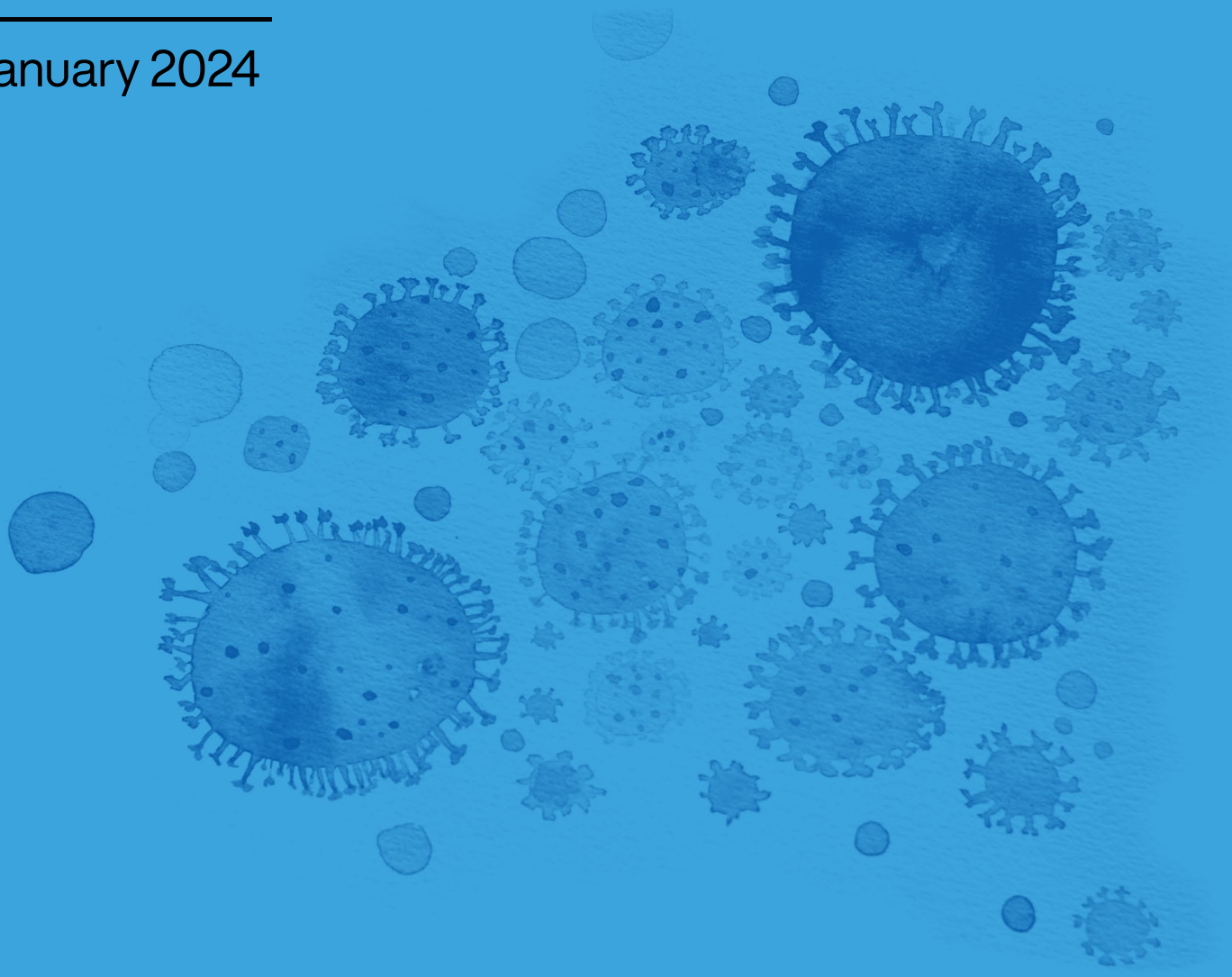
NIHR Policy Research Programme Reviews Facility

Supporting national policy development and implementation

Treatment and rehabilitation of Long COVID

A scope of the literature: update

January 2024



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Treatment and rehabilitation of Long COVID: A scope of the literature. Update January 2024

Raine G, Khouja C, Harden M, Sutcliffe K, Sowden A

January 2024

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Summary

- We identified 21 randomised controlled trials published between September and December 2023 that were focused on Long COVID treatment or rehabilitation. Across our seven reports produced to date, we have identified and assessed 106 trials published between January 2022 and December 2023.
- Eight of the 21 trials focused on treating generalised or multiple symptoms of Long COVID/Post COVID condition. Four trials had a primary focus on persistent problems with the sense of smell or taste (olfactory/gustatory dysfunction) and three others evaluated treatments specifically for fatigue. Two trials had a focus on respiratory or cardiovascular function and physical fitness; one of which also focused on post COVID anxiety and depression. Other trials focused on individuals with post COVID depressive symptoms (n=1); post COVID gastro-oesophageal reflux disease (n=1); and persistent memory impairment (n=1). One trial focused on improving the resilience and quality of life of individuals with Long COVID.
- Two trials were rated positively for 12 out of the 13 quality criteria that we assessed. Three trials met 11 criteria and three others met ten criteria. The remaining 13 trials gained a positive rating for between three and nine criteria.

Introduction

This is the seventh 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 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.

Searches were limited to studies added to the databases or published in 2022 or 2023, and no language restrictions were applied. Preprints were removed from the searches in MEDLINE and Embase. A new subject heading for Long COVID (Post-COVID-19 Conditions/) was available in PsycINFO for this update, so was added to the search strategy for PsycINFO. 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 18).

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 reports 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 26).

Key findings

We screened 417 records and included 21 RCTs that had been published since September 2023. [(4-24)] The number of included trials in this update is the largest since we began producing our reports in July 2022. The most trials we included in any of our previous six reports was 18. [(25, 26)] The flow of studies through the current update is shown in Appendix 3 (page 27). Table 1 (page 7) presents the aim(s) and key characteristics of the 21 trials.

Interventions

Eight trials focused on individuals experiencing generalised or multiple symptoms of Long COVID/Post COVID condition, typically including fatigue, lack of energy and dyspnoea. [(4, 7, 8, 13, 15-17, 21)] Four of the nine trials evaluated telerehabilitation programmes, [(4, 7, 8, 17)] one of which was aimed at young women only. [(4)] One of the eight trials focused on a therapeutic physical exercise programme involving in-person or home-based training. [(21)] One trial assessed water and land-based exercise sessions, specifically for children. [(15)] Another trial evaluated the use of acupuncture together with complex rehabilitation methods compared to complex rehabilitation methods only. These comprised a combination of respiratory gymnastics, massage, myorelaxation, physical therapy, speleotherapy, exercise equipment, aerosol therapy, oxygen cocktail, magnetotherapy, amplipulse therapy,

ultrawave frequencies, ultrasound therapy, ultraviolet irradiation, shungite therapy, inhalation, and outdoor walks. [16] The remaining trial evaluated the effect of the multimodal anti-depressant vortioxetine. [13]

Four of the 21 trials had a primary focus on persistent problems with the sense of smell or taste and investigated the effectiveness of various potential treatments: photo-biomodulation, transmucosal irradiation of blood, and B-complex supplementation; [6] intranasal injection of platelet-rich plasma; [9] alpha-lipoic acid and olfactory training; [10] and the antiepileptic drug gabapentin. [12] Three trials evaluated treatments specifically for fatigue and lack of energy: Brainmax (coordination complex with succinate acid anion); [23] creatine supplementation [22] and individualized homeopathic medicines. [20] One of these three trials focused on post-COVID fatigue syndrome and required participants to have fatigue plus one other persistent COVID symptom. [22]

Two other trials assessed treatments for individuals who had problems with respiratory or cardiovascular function and physical fitness. [11, 19] One of these trials focused on incentive spirometer-based breathing exercises and also assessed their effect on post COVID symptoms of anxiety and depression. [11] The other trial compared the efficacy of beta blockers and ivabradine (sinus node inhibitor) in treating post COVID inappropriate sinus tachycardia. [19]

Other trials assessed the effectiveness of donepezil hydrochloride (acetylcholine esterase inhibitor) for persistent memory impairment; [18] and celecoxib monotherapy for post COVID depressive symptoms. [5] One trial examined modified diaphragmatic training as treatment for gastro-oesophageal reflux disease after COVID-19. [24] The final trial assessed the effectiveness of acceptance and commitment therapy for improving resilience and the health-related quality of life in people with post-acute COVID-19 syndrome. [14]

Eight of the 21 RCTs in the current update evaluated interventions incorporating an exercise component and/or breathing training aimed at improving respiratory and/or physical fitness-related outcomes. This is similar to the proportion included in two previous reports - April 2023 (eight out of 18 RCTs) [25] and July 2022 (six out of 14 RCTs). [26] The proportion of included trials in the current update that focused on the treatment of olfactory/gustatory dysfunction (four out of 21 RCTs) is the lowest since our January 2023 report (two out of 12 RCTs). [27]

Participants

Ten trials recruited participants who had experienced persistent effects for at least four weeks after the onset of COVID symptoms or diagnosis. [4, 6-10, 12, 13, 17, 20] In seven of the ten trials, participants had persistent effects for at least 12 weeks after symptom onset or diagnosis. [4, 9, 10, 12, 13, 17, 20] Two other trials focused on individuals who tested positive for COVID-19, or were diagnosed, within the previous three months [22] and six months. [24]

Two trials recruited individuals more than four weeks [15] and 12 weeks after COVID-19 infection. [21] Participants in two other trials reported persistent symptoms after having COVID-19 in the previous eight weeks [11] and 12 to 52 weeks. [23] One study recruited individuals 20 days or more after the onset of COVID-19 symptoms, or at least seven days after they last experienced symptoms (excluding symptoms of depression). [5] In two trials, participants had persistent effects for at least four weeks after hospitalisation [14] or hospital discharge. [18] In the remaining two trials, the population comprised individuals with a history of COVID-19, but no time related details were reported. [16, 19]

Countries

Three trials were conducted in India; [11, 19, 20] Iran; [5, 14, 18] and Spain; [8, 17, 21] and two trials were conducted in Brazil. [6, 10] One trial was conducted in Canada; [13] Germany; [7] Indonesia; [24] Kazakhstan; [16] Poland; [15] Russia; [23] Saudi Arabia; [4] Serbia; [22] Turkey; [9] and the USA. [12]

Trial quality

Assessments of the trials against the JBI criteria are provided in Table 2 (page 13). None of the trials were assessed as having a low risk of bias for all 13 appraisal criteria. We rated two trials positively for 12 out of the 13 criteria. [5, 22] In these two trials, we could not tell if there was blinding of the personnel who administered the intervention (Q5) [5] or assessed outcomes (Q6). [22]

We rated three trials positively for 11 out of the 13 criteria. [10, 12, 13] In one of the three trials, we were unclear if a true method of randomisation had been used (Q1). [13] In another, 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). [12] In the third trial, we could not tell if there was blinding of the personnel who assessed outcomes (Q6). [10] In all three studies, the researchers also only analysed the data of participants who completed the trial and therefore we could not give a positive rating for the use of an Intention To Treat (ITT) analysis (Q9).

Three trials met ten criteria; [4, 8, 20] and 13 trials were rated positively for between three and nine criteria. [6, 7, 9, 11, 14-19, 21, 23, 24] A number of common issues were identified across the 16 trials that met 10 or fewer criteria. For example, it was unclear if an appropriate statistical analysis had been conducted in 11 of the 16 trials as no information was provided about the sample size requirements of the study (Q12). [6, 7, 9, 11, 14, 16, 18-20, 23, 24]

In nine of the 16 trials we could not tell if an appropriate procedure had been used for allocation concealment (Q2). [6, 7, 9, 14, 17-19, 21, 23] We were also unable to tell if an appropriate method of randomisation had been used for allocating participants to treatment groups in seven trials (Q1). [4, 6, 9, 14, 19, 21, 23] In another trial, an appropriate method of randomisation was used (rolling of a die), but a proportion of participants could not be randomised and were instead allocated to an active control group (n=30, 13%). There was also an untreated 'comparison group', which were not randomised. The authors described the study as a 'partially randomized controlled trial'. [7]

In seven trials, an ITT analysis was not conducted [6, 8, 11, 15, 17, 18, 21] and in three other studies, we could not tell if it had been used. [7, 14, 19]

In three trials that we rated positively for nine [15, 17] or ten [4] of the 13 criteria, there was no blinding of trial participants (Q4) and the personnel who administered the treatment (Q5). However, the nature of the intervention in these trials is likely to have precluded the use of blinding as all three evaluated telerehabilitation or other exercise-based programmes.

It was unclear whether trial participants were blinded in four of the remaining 13 trials (Q4). [6, 19, 23, 24] In seven of the trials, we could not tell if there was blinding of the personnel who administered the treatment (Q5) [8] and/or the outcome assessors (Q6). [6, 7, 9, 14, 19, 23]

In six of the 12 trials, there was no blinding of participants [8] and/or the personnel who administered the treatment. [7, 9, 14, 18, 21] In another two trials, there was no blinding of trial participants, the personnel who administered the treatment or outcome assessors. [11, 16] Neither the personnel who administered the treatment or assessed outcomes were blinded in one trial. [20] Again, the nature of the intervention in some of these 12 studies may have prevented the use of blinding.

Conclusion

To conclude, in this evidence scan, we identified 21 RCTs published between September and December 2023 that examined interventions for the treatment or rehabilitation of people with Long COVID. Across our seven reports produced to date, we have now identified and assessed 106 trials published since January 2022. Eight trials in the current update focused on treating generalised or multiple symptoms of Long COVID/Post COVID condition. Four trials had a primary focus on treating persistent problems with the sense of smell or taste. Other trials focused on fatigue/lack of energy (n=3); cardiovascular function/physical fitness (n=2), one of which also had a focus on post COVID anxiety and depression; post COVID depressive symptoms only (n=1); post COVID gastro-oesophageal reflux disease (n=1); and persistent memory impairment (n=1). One trial focused on improving the resilience and quality of life of individuals with Long COVID. Trial quality varied, with two rated positively for 12 out of the 13 criteria. Three trials met 11 criteria and another three met 10 criteria. The remaining 13 trials gained positive ratings for between three and nine criteria.

Table 1: Study characteristics (n=21)

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
Alsharidah (2023) [4] Saudi Arabia	To examine the impact of telerehabilitation training on exercise capacity, lung function, and health-related quality of life in comparison to no rehabilitation for post-COVID-19 symptoms in adult females	General/multiple: post-COVID symptoms	After symptom onset or diagnosis: mean 4.5 months after diagnosis	Female only (48)	Pulmonary/respiratory or cardiovascular function: Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 second (FEV1) Physical fitness: six-minute walk test Quality of life: SF-36	Written standardised educational instructions from physiotherapists, and information on COVID-19
Ansari (2023) [5] Iran	To investigate the potential beneficial effect of celecoxib monotherapy on depressive symptoms after Coronavirus disease (COVID-19)	Neuropsychiatric: moderate depressive symptoms	After onset or recovery: at least 20 days after initiation of COVID-19 symptoms or seven days after resolution of symptoms	Mixed (62 randomised; 56 completed) 39% female (24/62)	Psychological: Hamilton Depression Rating Scale (HDRS) Feasibility, tolerability and/or safety: side-effects checklist	Placebo
Cardoso (2023) [6] Brazil	To evaluate the efficacy of photo-biomodulation, transmucosal laser irradiation of blood, and B-complex supplementation in patients with long-term taste and smell impairment triggered by COVID-19	Olfactory and/or gustatory dysfunction	After symptom onset or diagnosis: over two months since positive test	Mixed (50 randomised; 39 analysed) 68% female (34/50)	Olfactory and/or gustatory function: self-reported smell and taste	Sham laser

Derksen (2023) [7] Germany	To assess whether patients who received a health care facilitation programme, including medical internet support from human personal pilots and digital interventions (with or without personalisation), would experience fewer symptoms and have higher work ability and social participation than an untreated comparison group	General/multiple symptoms: more than three of 14 symptoms (e.g., fatigue, muscle pain, or respiratory problems), with severity of two or more on a scale from 0 to 3	After symptom onset or diagnosis: diagnosed more than four weeks ago	Mixed (1020) 75% female (763/1020)	General or multiple symptoms/clinical outcomes: symptom severity (measured using a scale developed for the project); work ability (single item from the Work Ability Index); social participation (12-item questionnaire)	One active control group who received all personal support and digital interventions, but no diagnostic assessment One comparison group who received no treatment (care as usual)
Espinoza-Bravo (2023) [8] Spain	To compare the short-term effects of functional versus aerobic exercises, both combined with breathing techniques, in telerehabilitation on Long COVID symptoms	General/multiple symptoms at least one of three persistent symptoms - fatigue, dyspnoea or functional limitation	After symptom onset or diagnosis: symptoms for at least six weeks after positive test	Mixed (48 randomised; 43 completed) 79% female (34/43)	Fatigue: Fatigue Assessment Scale (Spanish)	Two interventions compared: functional vs aerobic exercise; no other comparator
Evman (2023) [9] Turkey	To investigate the efficacy of intranasal platelet-rich plasma injection on the olfactory cleft of patients with post-COVID olfactory dysfunction lasting over one year, who were unresponsive to common treatments	Olfactory and/or gustatory dysfunction	After symptom onset or diagnosis: one year or more after test-confirmed infection	Mixed (25) 52% female (13/25)	Olfactory and/or gustatory function: Connecticut Chemosensory Clinical Research Center (CCCRC) test	No additional treatment
Figueiredo (2024) [10] Brazil	To assess the effect of alpha-lipoic acid as an adjuvant treatment of olfactory training on the improvement of smell loss in post-COVID-19 patients	Olfactory and/or gustatory dysfunction	After symptom onset or diagnosis: three months or more after positive test	Mixed (128 randomised, 100 analysed)	Olfactory and/or gustatory function: CCCRC test; and visual analogic scale (VAS) score	Placebo (starch) with olfactory training

				82% female (82/100)		
Gudivada (2023) [11] India	To determine the rates of new-onset anxiety and depression in patients with restrictive or obstructive lung disease after COVID-19 infection and to assess the improvement in pulmonary functions and anxiety/depression scores after prescribing incentive spirometer-based breathing exercises	Respiratory or cardiovascular function or physical fitness: Respiratory complaints (dyspnoea or cough); pulmonary function assessment abnormalities	Unclear/not stated: within eight weeks of acute COVID-19 illness	Mixed (35 randomised; 34 completed) 23% female (8/35)	Pulmonary/respiratory or cardiovascular function: Pulmonary function test (PFT), including measures such as FEV1; FVC; and peak expiratory flow rate Psychological: Generalized Anxiety Disorder scale (GAD-7); Hamilton Anxiety Rating Scale (HARS); and Patient Health Questionnaire (PHQ-9)	Standard care: pharmacotherapy or behavioural therapy
Mahadev (2023) [12] USA	To evaluate the efficacy of oral gabapentin on olfactory function and olfaction-related quality of life in patients with COVID-19-induced olfactory dysfunction	Olfactory and/or gustatory dysfunction	After symptom onset or diagnosis: diagnosis of olfactory dysfunction lasting at least three months, associated with COVID-19 infection	Mixed (68 randomised; 41 completed) 75% female (51/68)	Olfactory and/or gustatory function: Clinical Global Impression of Improvement (CGI-I) (in smell or parosmia)	Placebo
McIntyre (2023) [13] Canada	To determine the impact of vortioxetine on objective measures of cognition, self-reported mood-related symptoms, and health-related quality of life in adults meeting the WHO criteria for post-COVID condition	General/multiple symptoms: diagnosis of PCC (WHO criteria)	After symptom onset or diagnosis: usually occurring three months from the onset of COVID-19, with symptoms that last for at least two months	Mixed (149 randomised; 141 completed) 66% female (98/149)	Cognitive: Digital Symbol Substitution Test (DSST)	Placebo

Nikrah (2023) [14] Iran	To examine the effectiveness of acceptance and commitment therapy on resilience and health-related quality of life of post-acute COVID-19 syndrome patients	Quality of life: Connor-Davidson Resilience Scale (CD-RISC) less than 16 and WHO's Quality of Life (WHOQOL-BREF) less than 75	After discharge: 30 days since hospitalisation	Mixed (30) 60% female (18/30)	Quality of life: Connor-Davidson Resilience Scale (CD-RISC) and WHO's Quality of Life (WHOQOL-BREF) questionnaire	No psychological intervention
Ogonowska-Slodownik (2023) [15] Poland	To determine the effectiveness of water-based and land-based exercise training programmes on exercise capacity, fatigue, and health-related quality of life in children with post-COVID-19 condition	General/multiple symptoms: typical of Long COVID including fatigue, short of breath	Unclear/not stated At least one month after infection	Mixed (86 randomised; 74 completed) 58% female (43/74)	Physical fitness: modified Balke treadmill protocol Fatigue: Polish adaptation of the Cumulative Fatigue Symptoms Questionnaire (CFSQ) for adolescents (also called the Cumulative Fatigue Symptoms Index)	No exercise - advised to not alter their current exercise routine
Omarova (2023) [16] Kazakhstan	To evaluate the effectiveness of complex rehabilitation methods (CRM) with and without acupuncture in a hospital setting, as well as to evaluate the effectiveness of CRMs in post-COVID-19 condition and their further widespread use to promote rapid recovery	General/multiple symptoms: post-COVID condition (PCC)	Unclear/not stated: clinical diagnosis of PCC	Mixed (160) 76% female (121/160)	Pulmonary/respiratory or cardiovascular function: Modified Medical Research Council Modified Dyspnea Scale (MDS) Physical fitness: six-minute walking test, and the Borg scale Performing daily activities: Barthel Index	Complex rehabilitation methods, which consisted of respiratory gymnastics, massage, myorelaxation, physical therapy, speleotherapy, exercise equipment, aerosol therapy, oxygen cocktail, magnetotherapy, amplipulse, ultrawave frequencies, ultrasound therapy, ultraviolet irradiation, shungite therapy, inhalation, and outdoor walks
Pleguezuelos (2023) [17]	To evaluate the effects of a 15-week telerehabilitation	General/multiple symptoms: post-	After symptom onset or diagnosis:	Mixed (150 randomised;	Pulmonary/respiratory or cardiovascular function:	No supervised telerehabilitation

Spain	programme and a detraining period on cardiorespiratory fitness and mechanical efficiency in patients with post-COVID-19 sequelae	COVID-19 symptoms, mainly dyspnoea, persistent fatigue, and muscle weakness	suffering from post-COVID sequelae more than three months from the onset of symptoms	131 completed) 43% female (56/131)	cardiopulmonary exercise test - including measures such as VO2 peak	programme; routine daily life activities
Pooladgar (2023) [18] Iran	To investigate the impact of donepezil hydrochloride on post-COVID memory impairment	Cognitive function: memory impairment	After discharge: discharged from the hospital for at least one month	Mixed (38 randomised; 25 completed) 56% female (14/25)	Psychological: General Health Questionnaire (GHQ-28) Cognitive: Wechsler Memory Scale-Revised (WMS-R)	Under observation without any active intervention
Raoof (2022) [19] India	To compare the efficacy of beta blockers and ivabradine in controlling the heart rate in post COVID-19 associated inappropriate sinus tachycardia	Respiratory or cardiovascular function or physical fitness: inappropriate sinus tachycardia (IST)- resting heart rate over 100 beats per minute (bpm) or medium Holter ECR heart rate over 90 bpm	Unclear/not stated: had a history of COVID-19	Mixed (48) 46% female (22/48)	Pulmonary/respiratory or cardiovascular function: heart rate (resolution of IST)	Two drugs compared: ivabradine versus metoprolol (a beta-blocker); no other comparator
Saha (2023) [20] India	To detect the difference between individualised homeopathic medicines and placebo in the treatment of post-COVID-19 fatigue in adults	Fatigue/lack of energy	After symptom onset or diagnosis: three months after onset of COVID-19, with symptoms for two months or more	Mixed (60 randomised; 53 completed) 53% female (32/60)	Fatigue: Fatigue Assessment Scale (FAS) score	Placebo
Senen (2023) [21] Spain	To assess the role a therapeutic physical exercise programme in patients with post-acute COVID syndrome and exercise intolerance	General/multiple symptoms: post-acute COVID symptoms, including asthenia and dyspnoea on exertion	Unclear/not stated: more than 12 weeks after infection	Mixed (50 randomised; 37 completed)	Pulmonary/respiratory or cardiovascular function: change in peak VO2, and percentage of the predicted	Recommendations for physical exercise and healthy habits, based on recommendations for the general population

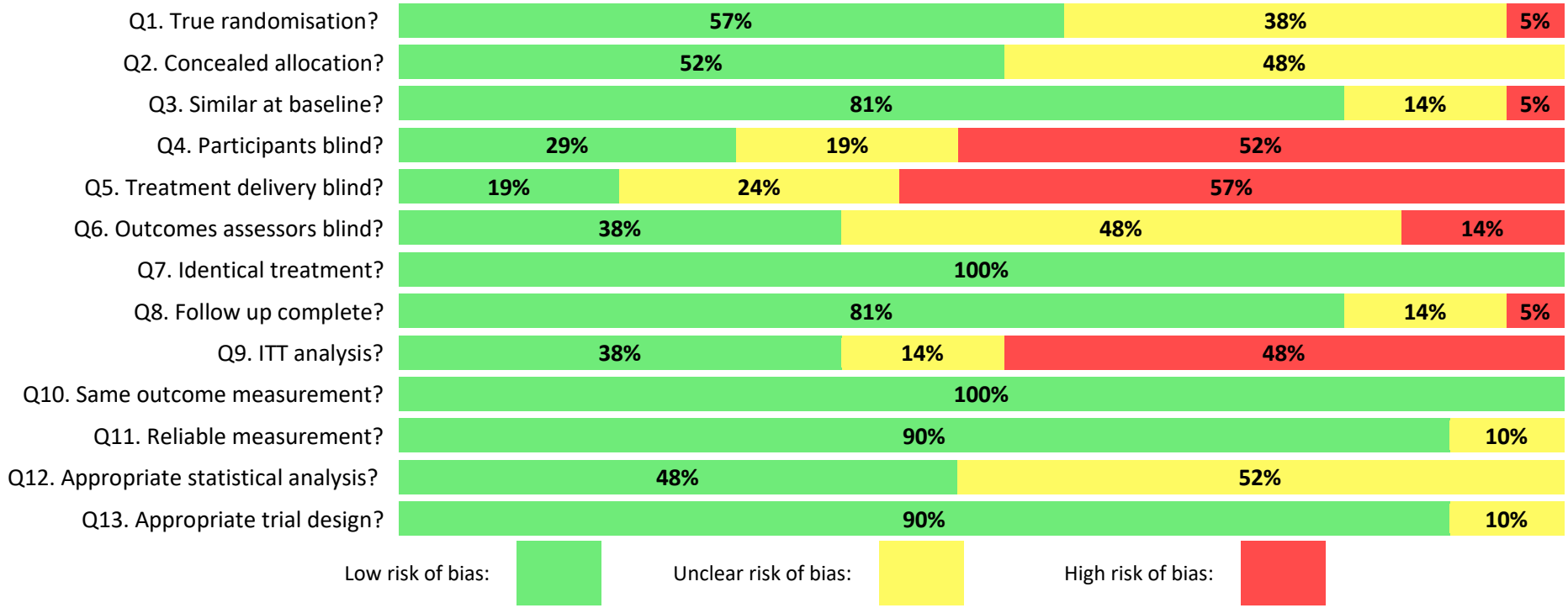
				73% female (27/37)	value, on cardiopulmonary exercise testing (CPET)	
Slankamenac (2023) [22] Serbia	To analyse the effects of six-month creatine supplementation on patient- and clinician-reported outcomes, and tissue creatine levels in patients with post-COVID-19 fatigue syndrome	Fatigue/lack of energy and at least one COVID-19-related symptom, including anosmia, ageusia, breathing difficulties, lung pain, body aches, headaches, or difficulty concentrating	After symptom onset or diagnosis: within three months of positive test	Mixed (12) 50% female (6/12)	Change in vastus medialis (thigh muscle) creatine levels; also measured fatigue and fatigue syndrome-related symptoms (Multidimensional Fatigue Inventory, MFI-20 test)	Placebo (Inulin, a pre-biotic dietary fibre)
Tanashyan (2023) [23] Russia	To assess the efficacy of coordination complex with succinate acid anion therapy (Brainmax) in patients with post-COVID asthenic syndrome	Fatigue/lack of energy	Unclear/not stated: more than 12 weeks, but less than 12 months prior history of COVID-19	Mixed (30) 80% female (24/30)	Fatigue: Multidimensional Fatigue Inventory (MFI-20), and Fatigue Assessment Scale (FAS-10) Cognitive: Montreal Cognitive Assessment (MoCA), and structural and functional MRI scans	Placebo
Widjanantie (2023) [24] Indonesia	To examine the effectiveness of modified diaphragmatic training for improving symptoms in adults with gastro-oesophageal reflux disease after COVID-19	Other: gastro-oesophageal reflux disease	After symptom onset or diagnosis: diagnosed with COVID less than six months before the study	Mixed (50) 50% female (25/50)	Pulmonary/respiratory or cardiovascular function: diaphragmatic excursion; and maximum inspiratory pressure Other: Gastroesophageal Reflux Disease Questionnaire score	Standard diaphragmatic training

Table 2: JBI risk of bias assessment

First author (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?
Alsharidah (2023)	?	+	+	-	-	+	+	+	+	+	+	+	+
Ansari (2023)	+	+	+	+	?	+	+	+	+	+	+	+	+
Cardoso (2023)	?	?	?	?	?	?	+	+	-	+	?	?	+
Derksen (2023)	-	?	+	-	-	?	+	-	?	+	?	?	?
Espinoza-Bravo (2023)	+	+	+	-	?	+	+	+	-	+	+	+	+
Evman (2023)	?	?	+	-	-	?	+	+	+	+	+	?	+
Figueiredo (2024)	+	+	+	+	+	?	+	+	-	+	+	+	+
Gudivada (2023)	+	+	?	-	-	-	+	?	-	+	+	?	+
Mahadev (2023)	+	?	+	+	+	+	+	+	-	+	+	+	+
McIntyre (2023)	?	+	+	+	+	+	+	+	-	+	+	+	+
Nikrah (2023)	?	?	+	-	-	?	+	?	?	+	+	?	+
Ogonowska-Slodownik (2023)	+	+	+	-	-	?	+	+	-	+	+	+	+
Omarova (2023)	+	+	?	-	-	-	+	+	+	+	+	?	+
Pleguezuelos (2023)	+	?	+	-	-	+	+	+	-	+	+	+	+
Pooladgar (2023)	+	?	+	-	-	+	+	+	-	+	+	?	+
Raoof (2022)	?	?	+	?	?	?	+	?	?	+	+	?	?

Saha (2023)	+	+	+	+	-	-	+	+	+	+	+	?	+
Senen (2023)	?	?	+	-	-	?	+	+	-	+	+	+	+
Slankamenac (2023)	+	+	+	+	+	?	+	+	+	+	+	+	+
Tanashyan (2023)	?	?	+	?	?	?	+	+	+	+	+	?	+
Widjanantie (2023)	+	+	-	?	-	+	+	+	+	+	+	?	+

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



NB: figures may not add up to 100% due to rounding. In our reports, we adopt a 'once randomised, always analysed' approach to assessing the use of an ITT analysis (Q9), which is consistent with previous research and guidance. [28-30]

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

27. 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.

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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 2023
Date searched: 4th December 2023
Records retrieved: 1262

Although 1561 records were identified overall in CENTRAL, trial register records were removed from this set, leaving a total of 1262 records downloaded for this update.

#1 MeSH descriptor: [Post-Acute COVID-19 Syndrome] this term only 78
#2 MeSH descriptor: [COVID-19] this term only and with qualifier(s): [complications - CO] 236
#3 MeSH descriptor: [COVID-19] this term only 4966
#4 MeSH descriptor: [SARS-CoV-2] this term only 2458
#5 MeSH descriptor: [Syndrome] this term only 6420
#6 MeSH descriptor: [Survivors] this term only 1560
#7 #3 or #4 5180
#8 #5 or #6 7975
#9 #7 and #8 60
#10 #1 or #2 or #9 344
#11 (long next (covid* or covid-19 or covid19 or coronavirus) or longcovid*):ti,ab,kw 360
#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 664
#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 1175
#14 PASC:ti,ab,kw 57
#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 143
#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 34
#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 99
#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 731
#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 242
#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 1060
#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 543
#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 186
#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 293
#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 161
#25 {OR #11-#24} 2503
#26 #10 or #25 with Cochrane Library publication date Between Jan 2022 and Dec 2023, in Trials 1548

#27 #10 or #25 with Publication Year from 2022 to 2023, in Trials 1428
#28 #26 or #27 1561

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 01, 2023
Date searched: 4th December 2023
Records retrieved: 889

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/ (2709)
2 COVID-19 post-intensive care syndrome.mp. (6)
3 COVID-19/co [Complications] (16222)
4 COVID-19/ or SARS-CoV-2/ (253596)
5 Syndrome/ (123318)
6 Survivors/ (30928)
7 5 or 6 (154125)
8 4 and 7 (1080)
9 1 or 2 or 3 or 8 (18213)
10 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,kf,ot,bt. (4358)
11 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,kf,ot,bt. (9454)
12 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (946)
13 PASC.ti,ab,kf,ot,bt. (810)
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. (2689)
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. (326)
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. (3378)
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. (2240)
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. (4079)
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. (94)
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. (259)

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. (3077)
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. (9231)
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. (2897)
24 or/10-23 (32628)
25 9 or 24 (45338)
26 randomized controlled trial.pt. (604235)
27 controlled clinical trial.pt. (95474)
28 randomi#ed.ab. (748248)
29 placebo.ab. (243680)
30 clinical trials as topic.sh. (201488)
31 randomly.ab. (422276)
32 trial.ti. (298254)
33 26 or 27 or 28 or 29 or 30 or 31 or 32 (1612464)
34 exp animals/ not humans.sh. (5175557)
35 33 not 34 (1486919)
36 25 and 35 (1411)
37 limit 36 to yr="2022 -Current" (892)
38 (2022* or 2023*).dt. (3063011)
39 36 and 38 (852)
40 37 or 39 (900)
41 preprint.pt. (17574)
42 40 not 41 (889)

Embase
via Ovid http://ovidsp.ovid.com/
Date range: 1974 to 2023 December 01
Date searched: 4th December 2023
Records retrieved: 1378

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/ (6163)
2 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,kw,ot. (4499)
3 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,kw,ot. (12096)
4 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (864)
5 PASC.ti,ab,kw,ot. (1004)
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. (3270)
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. (402)

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. (3461)
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. (2745)
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. (5146)
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. (168)
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. (280)
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. (4438)
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. (12484)
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. (3529)
16 or/2-15 (40881)
17 1 or 16 (41484)
18 random$.ti,ab. (2004049)
19 factorial$.ti,ab. (48165)
20 crossover$.ti,ab. (91754)
21 cross-over$.ti,ab. (38140)
22 placebo$.ti,ab. (371347)
23 (doubl$ adj blind$).ti,ab. (247235)
24 (singl$ adj blind$).ti,ab. (32208)
25 assign$.ti,ab. (498390)
26 allocat$.ti,ab. (206084)
27 volunteer$.ti,ab. (297680)
28 Crossover Procedure/ (76088)
29 double blind procedure/ (213246)
30 Randomized Controlled Trial/ (795567)
31 single blind procedure/ (52660)
32 controlled clinical trial/ (471618)
33 or/18-32 (3104194)
34 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (6865139)
35 33 not 34 (2770548)
36 17 and 35 (2667)
37 limit 36 to yr="2022 -Current" (1859)
38 (2022$ or 2023$).dd. (1235271)
39 36 and 38 (708)
40 37 or 39 (1967)
41 (conference abstract or "conference review").pt. (4992469)
42 40 not 41 (1489)
43 limit 42 to "remove preprint records" (1378)

PsycINFO
via Ovid http://ovidsp.ovid.com/
Date range: 1806 to November Week 3 2023
Date searched: 4th December 2023
Records retrieved: 327

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 post-covid-19 conditions/ (140)
2 covid-19/ (28872)
3 coronavirus/ (5897)
4 syndromes/ (17796)
5 sequelae/ (3986)
6 2 or 3 (31294)
7 4 or 5 (21714)
8 6 and 7 (319)
9 1 or 8 (432)
10 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,id,ot. (240)
11 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,id,ot. (901)
12 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (45)
13 PASC.ti,ab,id,ot. (44)
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,id,ot. (189)
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,id,ot. (24)
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,id,ot. (356)
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,id,ot. (179)
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,id,ot. (260)
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,id,ot. (7)
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,id,ot. (19)
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,id,ot. (282)
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,id,ot. (511)
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,id,ot. (329)
24 or/10-23 (2641)
25 randomized clinical trials/ (504)
26 randomized controlled trials/ (1032)
27 clinical trials/ (12263)
28 clinical trial.md. (39577)

29 (randomi#ed or randomi#ation or randomi#ing).ti,ab,id. (111172)
30 randomly.ti,ab,id. (85012)
31 (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. (130920)
32 (groups or (control* adj3 group*)).ab. (619438)
33 ((control* or trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw. (19314)
34 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id. (29492)
35 trial.ti. (38907)
36 (placebo or sham).ti,ab,id,hw. (58889)
37 treatment outcome.md. (24196)
38 treatment effectiveness evaluation/ (28833)
39 mental health program evaluation/ (2433)
40 or/25-39 (821674)
41 9 or 24 (2797)
42 40 and 41 (402)
43 limit 42 to yr="2022 -Current" (269)
44 (2022$ or 2023$).up. (359417)
45 42 and 44 (318)
46 43 or 45 (327)

CINAHL Ultimate
via Ebsco https://www.ebsco.com/
Date range: Inception to 20231204
Date searched: 4th December 2023
Records retrieved: 678

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") 1,050
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*) 1,430
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*) 1,680
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)) 355
S5 TI PASC OR AB PASC 105
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)) 596

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)) 280
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)) 739
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)) 1,063
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)) 939
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)) 54
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)) 96
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)) 1,100
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)) 4,269
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)) 945
S16 (MH "Randomized Controlled Trials") 141,231
S17 (MH "Double-Blind Studies") 54,652
S18 (MH "Single-Blind Studies") 16,085
S19 (MH "Random Assignment") 82,423
S20 (MH "Pretest-Posttest Design") 54,275
S21 (MH "Cluster Sample") 5,369
S22 TI randomised OR randomized 146,374
S23 AB random* 404,523
S24 TI trial 188,421
S25 MH (sample size) AND AB (assigned OR allocated OR control) 4,452
S26 MH (placebos) 14,254
S27 PT (randomized controlled trial) 154,982
S28 AB (control W5 group) 147,194
S29 MH (crossover design) OR MH (comparative studies) 490,086
S30 AB (cluster W3 RCT) 503
S31 MH animals+ 104,987

S32 MH (animal studies) 155,406
S33 TI (animal model*) 3,898
S34 S31 OR S32 OR S33 251,441
S35 MH (human) 2,749,033
S36 S34 NOT S35 216,970
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 1,039,949
S38 S37 NOT S36 991,631
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 11,157
S40 S38 AND S39 1,003
S41 S38 AND S39 Limiters - Publication Date: 20220101-20231231 660
S42 (ZD 2022* or 2023*) 357,806
S43 S40 AND S42 237
S44 S41 OR S43 678

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

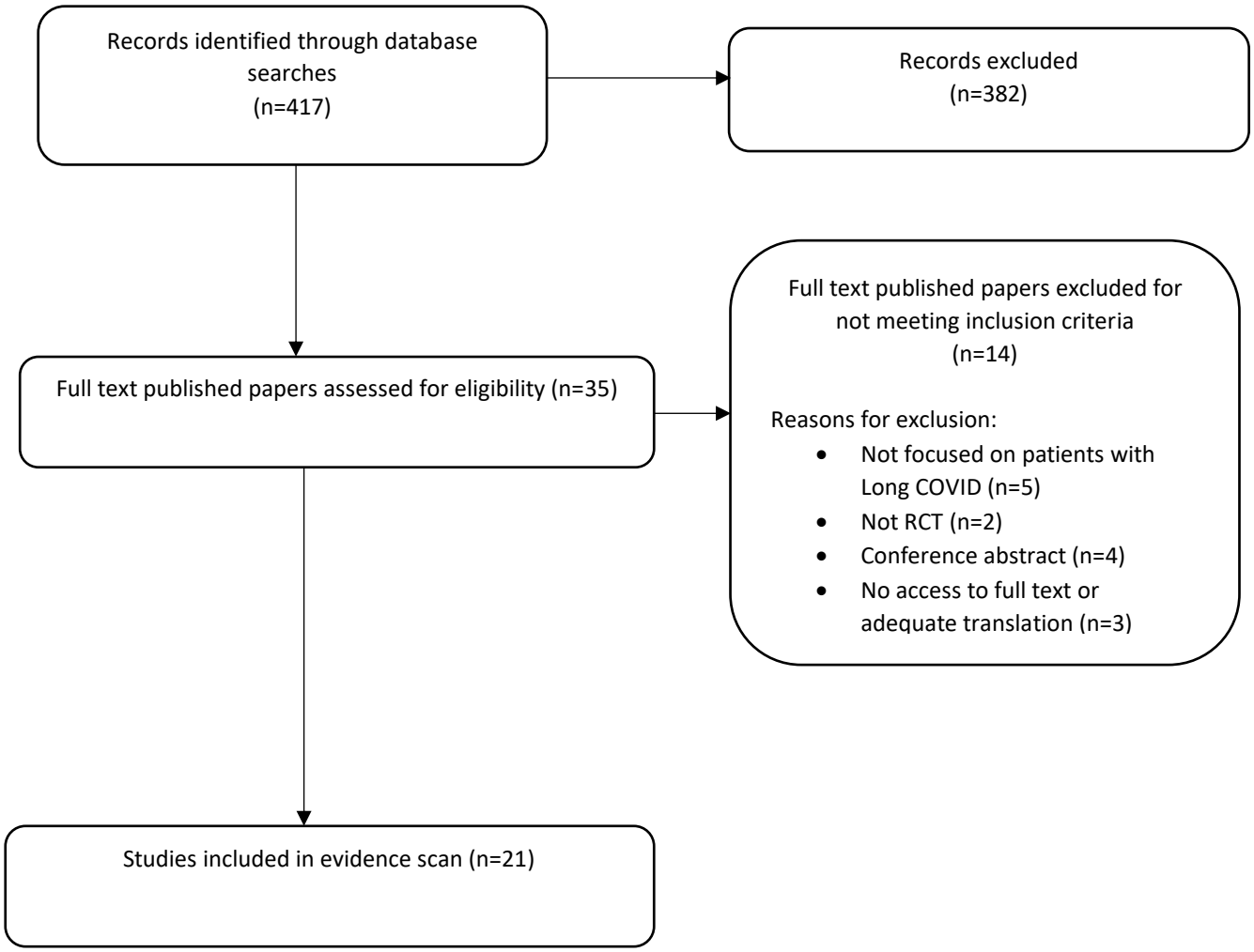
Q10 Were outcomes measured in the same way for treatment groups? Yes, No, Unclear, NA

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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