
Monograph:
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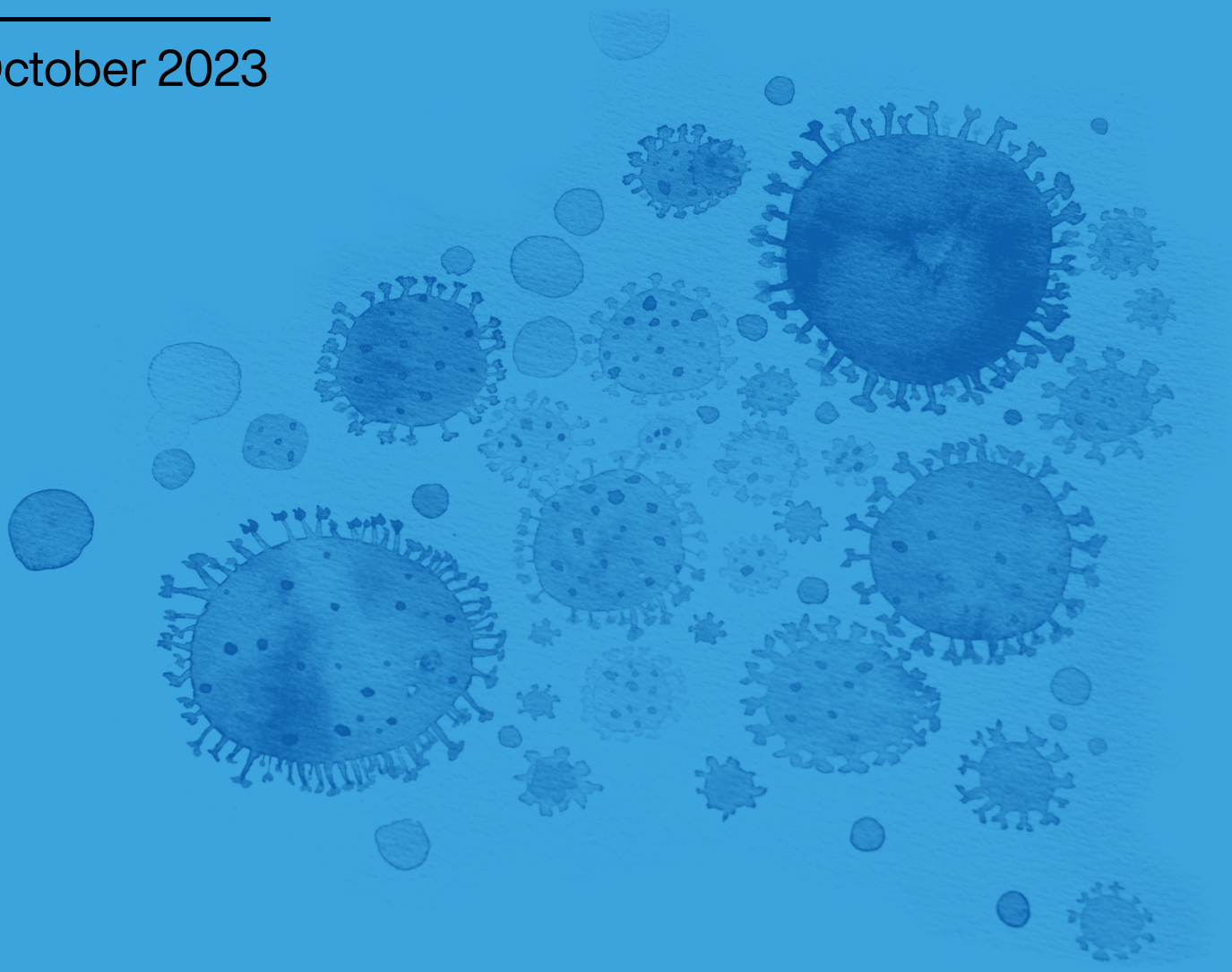
NIHR Policy Research Programme Reviews Facility

Supporting national policy development and implementation

Treatment and rehabilitation of Long COVID

A scope of the literature: update

October 2023



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London School of Hygiene & Tropical Medicine

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

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

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Summary

- We identified 12 randomised controlled trials published since early June 2023 that were focused on Long COVID treatment or rehabilitation. Across our six reports produced to date, we have identified and assessed 85 trials published between January 2022 and September 2023.
- Five of the 12 trials in the current update had a primary focus on treating persistent problems with the sense of smell or taste (olfactory/gustatory dysfunction). Other trials focused on individuals with multiple or non-specific Long COVID symptoms (n=2); respiratory health and physical fitness (n=2); cognitive dysfunction (n=1); and fatigue (n=1). One trial focused on cardiac dysfunction in individuals with persistent cognitive symptoms (n=1).
- One trial was rated positively for 12 out of the 13 quality criteria that we assessed. Three trials met 10 criteria and eight trials gained a positive rating for either eight or nine of the criteria.

Introduction

This is the sixth 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 June and September 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. 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 14).

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 22).

Key findings

We screened 324 records and included 12 RCTs that had been published since June 2023.[4-15] The number of included trials is the lowest since our January 2023 report, which also identified and assessed 12 studies.[16] The flow of studies through the current update is shown in Appendix 3 (page 23). Table 1 (page 6) presents the aim(s) and key characteristics of the 12 trials.

Interventions

Five of the 12 trials had a primary focus on persistent problems with the sense of smell or taste and investigated the effectiveness of various potential treatments- intranasal ethylene diamine tetra acetic acid;[4] oral vitamin A with olfactory training;[6]; co-ultramicronized palmitoylethanolamide with luteolin (umPEA-LUT, an anti-neuroinfammatory supplement) only or combined therapy (um-PEA-LUT plus olfactory training);[8] budesonide nasal irrigation with olfactory training;[9] and intranasal steroid injection (dexamethasone) with olfactory training.[10]

Two trials focused on individuals who had problems with cardiovascular function and physical fitness - dyspnoea[14] and decreased functional capacity.[7] Both trials evaluated exercise-based rehabilitation programmes, one of which involved telerehabilitation.[7]

Two trials focused on individuals with multiple or non-specific symptoms of Long COVID.[5, 15] One assessed the drugs hydroxychloroquine and clarithromycin for improving multiple ongoing respiratory symptoms.[5] The other evaluated an amygdala and insula retraining neuroplasticity programme (The Gupta program) with a primary focus on reducing fatigue.[15]

One trial evaluated anodal transcranial direct current stimulation as a treatment for persistent fatigue.[13] One trial examined the impact of hyperbaric oxygen therapy on the cardiac function of individuals with post-COVID-19 cognitive symptoms.[11] Another trial assessed the drug famotidine (a selective histamine H2 receptor antagonist) for treating persistent cognitive impairment.[12]

The proportion of included trials in the current update that focused on persistent problems with the sense of smell or taste (five out of 12 RCTs) is the largest since our October 2022 report (seven out of 11 RCTs).[17] In both of our last two reports (July and April 2023), five out of 18 trials assessed treatments for olfactory/gustatory dysfunction.[18, 19] Out of the 85 trials we have identified to date, a majority (60%) reported on various treatments for olfactory/gustatory dysfunction (n=25) or assessed interventions with a physical therapy component and/or breathing training (n=26).

Participants

Five trials recruited participants who had experienced persistent effects for at least four weeks after the onset of COVID symptoms or diagnosis.[6, 9-11, 13] In four of these five trials, the participants had persistent effects for at least 12 weeks after symptom onset or diagnosis.[6, 10, 11, 13] In the fifth trial, participants had experienced a decrease in their sense of smell for between 30 to 90 days after the onset of COVID-19 symptoms.[9]

In another five trials, participants had persistent effects for at least two weeks;[5] 12 weeks;[14, 15] and 24 weeks;[4, 8] after recovery from acute infection or hospital discharge. In another trial, individuals were invited to participate on the day of discharge.[7] The remaining trial recruited individuals 20 days or more after the onset of COVID-19 symptoms, and at least seven days after they last experienced any symptoms.[12]

Countries

Of the 12 included trials, two were conducted in Egypt;[4, 10] France;[9, 14] and Iran.[5, 12] One trial was conducted in Brazil;[7] Hong Kong;[6] Italy;[8] Israel;[11] Spain;[13] and the USA.[15]

Trial quality

Assessments of the trials against the JBI criteria are provided in Table 2 (page 10). None of the trials were assessed as having a low risk of bias for all 13 appraisal criteria. We rated one trial positively for 12 out of the 13 criteria.[12] We could not rate this trial positively for one criterion as it was unclear if an intention-to-treat (ITT) analysis had been conducted (Q9).

Three trials met 10 out of the 13 criteria[7, 11, 14] and eight trials were rated positively for either eight or nine criteria.[4-6, 8-10, 13, 15] A number of common issues were identified across the 11 trials that met 10 or fewer criteria. For example, it was unclear if an appropriate statistical analysis had been conducted in seven out of the 11 studies as no information was provided about the sample size requirements of the trial (Q12).[4, 5, 8, 10, 11, 14, 15] In five trials, we could not tell if an appropriate procedure had been used for allocation concealment (Q2).[4, 8, 9, 13, 15] In four trials, an ITT analysis was not conducted [6, 8, 11, 13] and in one other study, we could not tell if it had been used.[7]

It was unclear whether trial participants were blinded in three of the 11 trials (Q4).[4, 10, 15] In five trials, we could not tell if there was blinding of the personnel who administered the treatment (Q5),[4, 8, 10, 11] and/or those who assessed outcomes of interest (Q6).[10, 15]

In four of the 11 studies, there was no blinding of either trial participants or the personnel who administered the treatment.[5, 7, 9, 14] In another trial, there was no blinding of trial participants, the personnel who administered the treatment or outcome assessors.[6] In two trials, there was no blinding of the personnel who administered the treatment.[13, 15] However, the nature of the intervention in some of these trials potentially precluded the use of blinding, particularly those that evaluated physical therapy-based programmes.

To conclude, in this evidence scan, we identified 12 RCTs published between June and September 2023 that examined interventions for the treatment or rehabilitation of people with Long COVID. Across our six reports produced to date, we have now identified and assessed 85 trials published since January 2022. Five of the 12 trials in the current update had a primary focus on treating persistent problems with the sense of smell or taste (olfactory/gustatory dysfunction) Other trials focused on individuals with multiple or non-specific Long COVID symptoms (n=2);respiratory health and physical fitness (n=2); fatigue (n=1) and cardiac (n=1) or cognitive dysfunction (n=1). Trial quality varied, with one rated positively for 12 out of the 13 criteria, and three met 10 criteria. The remaining eight trials gained positive ratings for eight or nine criteria.

Table 1: Study characteristics (n=12)

First author (year) Country	Aim of study	Main symptom or effect experienced	Post COVID time	Participants' gender (n) and % female	Primary outcome(s) of interest	Comparator
Abdelazim (2023)[4] Egypt	To demonstrate the effect of intranasal ethylene diamine tetra acetic acid (EDTA) on improving olfactory dysfunction following COVID-19	Olfactory and/or gustatory dysfunction	After recovery: more than six months after negative test	Mixed (50) 62% female (31/50)	Olfactory and/or gustatory function: Sniffin Sticks test	Olfactory training alone
Bemanian (2023)[5] Iran	To evaluate hydroxychloroquine or clarithromycin to accelerate the improvement of prolonged respiratory symptoms in post-acute COVID-19 syndrome	General/multiple symptoms: symptoms such as shortness of breath, cough or pulmonary involvement on a CT scan	After recovery: two weeks after end of treatment	Mixed (34) 35% female (12/34)	Pulmonary/respiratory or cardiovascular function: shortness of breath, cough, laboratory tests, the six-min walk test, and spirometry	Placebo
Chung (2023)[6] Hong Kong	To evaluate the therapeutic efficacy of short-course oral vitamin A with olfactory training, delivered via novel aerosolisation diffusers, as an innovative treatment strategy in the management of persistent olfactory dysfunction in Long COVID patients	Olfactory and/or gustatory dysfunction	After diagnosis: confirmed test and three or more months of olfactory dysfunction	Mixed (26; 22 completed) 64% female (14/22)	Olfactory and/or gustatory function: Butanol Threshold Test	Two comparator groups: Olfactory training alone (usual care) Clinical observation for four weeks (control group)
da Silva (2023)[7]	To verify the effects of cardiopulmonary	Respiratory or cardiovascular	After discharge: participants	Mixed (67; 57 started and 51	Physical fitness: six-minute step test	A physical therapy session via

Brazil	telerehabilitation using functional and accessible exercises in individuals after COVID-19 hospital discharge	function or physical fitness: poor functional capacity	were invited to participate on the day of discharge	completed) 44% female (25/57)		videoconference on general health care (lifestyle and physical activity), with vital signs monitoring, and a diary to record daily physical activity
Di Stadio (2023)[8] [b] Italy	To investigate the relative efficacy of olfactory training with placebo, co-ultramicronised palmitoylethanolamide with luteolin (um-PEA-LUT, an anti-neuroinflammatory supplement) or combined therapy (um-PEA-LUT plus olfactory training) for treating chronic olfactory dysfunction from COVID-19	Olfactory and/or gustatory dysfunction	After recovery: over six months (180 days) of olfactory dysfunction after negative test	Mixed (250; 202 completed) 53% female (108/202)	Olfactory and/or gustatory function: Sniffin' Sticks test	Olfactory training with placebo
Hautefort (2023)[9] France	To assess the efficacy of budesonide nasal irrigation in addition to olfactory rehabilitation for managing non-severe COVID-19 patients with persistent hyposmia	Olfactory and/or gustatory dysfunction	After symptom onset: 30 to 90 days after the onset of symptoms	Mixed (123) 67% female (83/123)	Olfactory and/or gustatory function: ODORATEST score	Saline nasal irrigation with olfactory rehabilitation
Lasheen (2023)[10] Egypt	To study the effect of intranasal steroid injection (dexamethasone) with olfactory training in	Olfactory and/or gustatory dysfunction	After diagnosis: more than 12 weeks after diagnosis	Mixed (40) 55% female (22/40)	Olfactory and/or gustatory function: Olfactory disorder questionnaire	Nasal saline injections with olfactory training

	post-COVID olfactory dysfunction					
Leitman (2023)[11] Israel	To evaluate the effect of hyperbaric oxygen therapy on the cardiac function of post-COVID-19 patients	Post COVID-19 cognitive symptoms	After diagnosis: more than three months after confirmed mild-to-moderate symptomatic infection	Mixed (79; 72 completed and 60 analysed) 58% female (35/60)	Pulmonary/respiratory or cardiovascular function: Global Longitudinal Strain [a]	Sham therapy (21% oxygen by mask at 1.03 ATA for 90 minutes)
Momtazmanesh (2023)[12] Iran	To investigate the efficacy and safety of famotidine, (a selective histamine H2 receptor antagonist), for improving cognitive impairment, depression and anxiety symptoms observed after COVID-19 infection	Cognitive dysfunction	After diagnosis: at least 20 days since the onset of symptoms, and at least seven days since the last day of symptoms	Mixed (number starting trial unclear; 45 completed) 46% female (23/50)	Cognitive function: Mini-Mental State Examination	Placebo
Oliver-Mas (2023)[13] Spain	To assess the effects of anodal transcranial direct current stimulation on fatigue severity in a group of patients with post-COVID syndrome and chronic fatigue	Fatigue/lack of energy	After diagnosis: at least six months after positive test	Mixed (48; 47 analysed) 79% female (37/47)	Fatigue: Modified Fatigue Impact Scale score	Sham transcranial direct current stimulation
Romanet (2023)[14] France	To evaluate the effects of exercise training rehabilitation on dyspnoea and health-related quality of life measures in people with continuing respiratory discomfort following COVID-19-related acute	Respiratory or cardiovascular function or physical fitness: dyspnoea	After discharge: three or more months after discharge from ICU	Mixed (60) 38% female (23/60)	Pulmonary/respiratory or cardiovascular function: Multidimensional Dyspnoea Profile	Usual care: standard physiotherapy

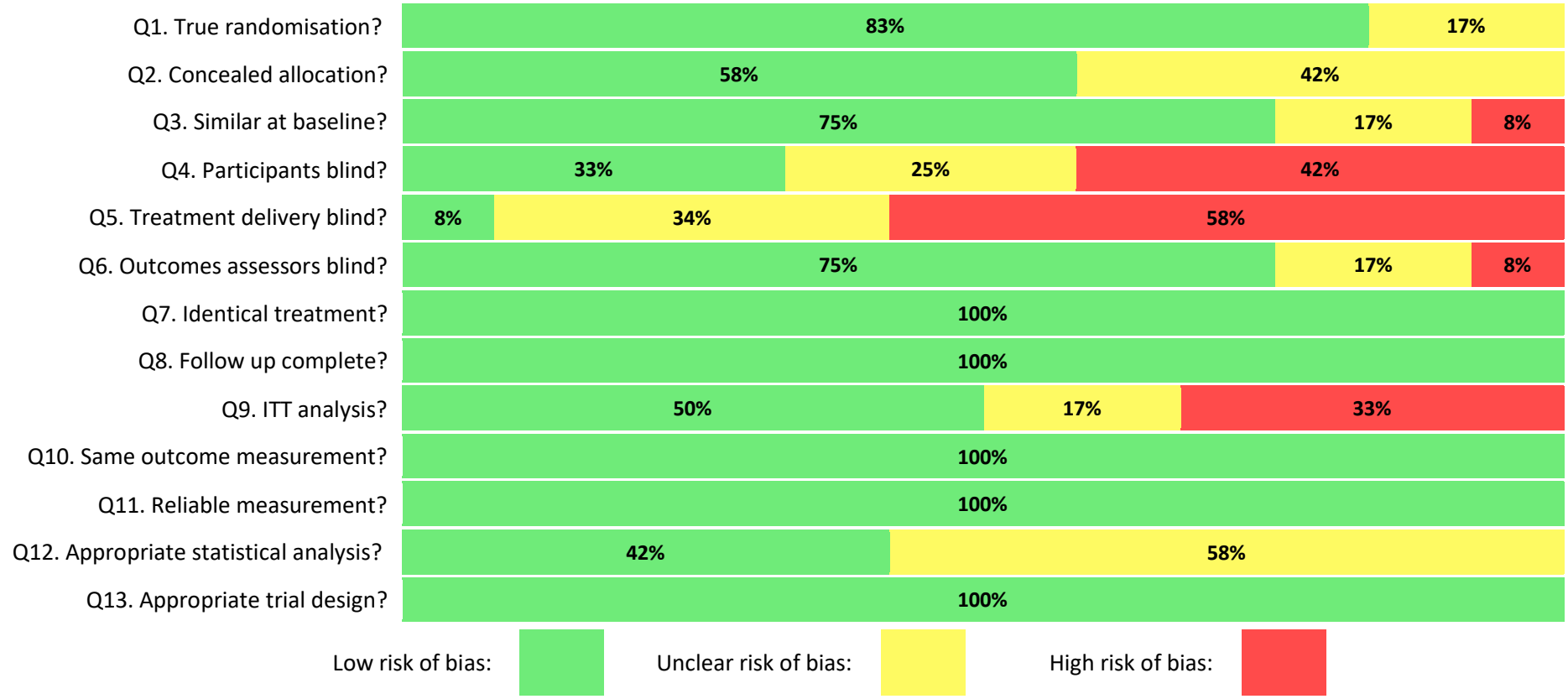
	respiratory distress syndrome					
Toussaint (2023)[15] USA	To test the effectiveness of an online Amygdala and Insula Retraining neuroplasticity programme (The Gupta program) in reducing prolonged symptoms of fatigue following COVID-19 infection	General/multiple symptoms: post-viral symptoms	After recovery: at least three months after an acute COVID-19 infection	Mixed (100; 42 completed) 86% female (86/100) (one non-binary and one declined to answer)	Quality of life: Short Form Health Survey (SF-36) Fatigue: Multidimensional Fatigue Inventory	Online educational programme for general health and well-being (12 weeks to wellness); which included general advice on diet, exercise, energy, nutrition, sleep, and other lifestyle interventions, as well as encouragement

[a] Findings related to cognitive dysfunction were reported in our October 2022 report.[17] [b] This trial has the same protocol identification number and evaluated the effect of the same supplement as two other studies we have included in previous reports.[18, 20] All three trials comprised a different number of participants and they did not recruit over the same time period; the recruitment period for two of the studies did overlap by eight months.

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?
Abdelazim (2023)	+	?	+	?	?	+	+	+	+	+	+	?	+
Bemanian (2023)	+	+	?	-	-	+	+	+	+	+	+	?	+
Chung (2023)	+	+	?	-	-	-	+	+	-	+	+	+	+
da Silva (2023)	+	+	+	-	-	+	+	+	?	+	+	+	+
Di Stadio (2023)	+	?	+	+	?	+	+	+	-	+	+	?	+
Hautefort (2023)	?	?	+	-	-	+	+	+	+	+	+	+	+
Lasheen (2023)	?	+	+	?	?	?	+	+	+	+	+	?	+
Leitman (2023)	+	+	+	+	?	+	+	+	-	+	+	?	+
Momtazmanesh (2023)	+	+	+	+	+	+	+	+	?	+	+	+	+
Oliver-Mas (2023)	+	?	-	+	-	+	+	+	-	+	+	+	+
Romanet (2023)	+	+	+	-	-	+	+	+	+	+	+	?	+
Toussaint (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

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Appendix 1 – search strategies

Cochrane Controlled Register of Trials (CENTRAL)
via Wiley http://onlinelibrary.wiley.com/
Issue: Issue 8 of 12, September 2023
Date searched: 4th September 2023
Records retrieved: 1075

Although 1351 records were identified overall in CENTRAL, trial register records were removed from this set, leaving a total of 1075 records downloaded for this update.

#1 MeSH descriptor: [Post-Acute COVID-19 Syndrome] this term only 59
#2 MeSH descriptor: [COVID-19] this term only and with qualifier(s): [complications - CO] 219
#3 MeSH descriptor: [COVID-19] this term only 4725
#4 MeSH descriptor: [SARS-CoV-2] this term only 2376
#5 MeSH descriptor: [Syndrome] this term only 6287
#6 MeSH descriptor: [Survivors] this term only 1543
#7 #3 or #4 4938
#8 #5 or #6 7825
#9 #7 and #8 54
#10 #1 or #2 or #9 305
#11 (long next (covid* or covid-19 or covid19 or coronavirus) or longcovid*):ti,ab,kw 307
#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 585
#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 1053
#14 PASC:ti,ab,kw 55
#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 135
#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 32
#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 95
#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 662
#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 212
#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 949
#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 475
#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 173
#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 266
#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 144
#25 {OR #11-#24} 2297
#26 #10 or #25 with Cochrane Library publication date Between Jan 2022 and Sep 2023, in Trials 1338

#27 #10 or #25 with Publication Year from 2022 to 2023, in Trials 1223
#28 #26 or #27 1351

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 September 01, 2023
Date searched: 4th September 2023
Records retrieved: 750

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/ (2364)
2 COVID-19 post-intensive care syndrome.mp. (5)
3 COVID-19/co [Complications] (15420)
4 COVID-19/ or SARS-CoV-2/ (243025)
5 Syndrome/ (122924)
6 Survivors/ (30613)
7 5 or 6 (153417)
8 4 and 7 (1035)
9 1 or 2 or 3 or 8 (17098)
10 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,kf,ot,bt. (3795)
11 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,kf,ot,bt. (8602)
12 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (843)
13 PASC.ti,ab,kf,ot,bt. (717)
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. (2440)
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. (312)
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. (3294)
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. (2075)
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. (3762)
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. (89)
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. (247)

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. (2911)
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. (8595)
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. (2695)
24 or/10-23 (30341)
25 9 or 24 (42505)
26 randomized controlled trial.pt. (599113)
27 controlled clinical trial.pt. (95416)
28 randomi#ed.ab. (734861)
29 placebo.ab. (241111)
30 clinical trials as topic.sh. (201200)
31 randomly.ab. (415708)
32 trial.ti. (291933)
33 26 or 27 or 28 or 29 or 30 or 31 or 32 (1591398)
34 exp animals/ not humans.sh. (5151321)
35 33 not 34 (1467252)
36 25 and 35 (1272)
37 limit 36 to yr="2022 -Current" (753)
38 (2022* or 2023*).dt. (2661262)
39 36 and 38 (714)
40 37 or 39 (761)
41 preprint.pt. (12841)
42 40 not 41 (750)

Embase
via Ovid http://ovidsp.ovid.com/
Date range: 1974 to 2023 September 01
Date searched: 4th September 2023
Records retrieved: 1183

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/ (5328)
2 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,kw,ot. (3943)
3 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,kw,ot. (10939)
4 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (781)
5 PASC.ti,ab,kw,ot. (912)
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. (3006)
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. (372)

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. (3356)
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. (2519)
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. (4729)
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. (162)
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. (266)
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. (4166)
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. (11538)
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. (3278)
16 or/2-15 (37814)
17 1 or 16 (38341)
18 random$.ti,ab. (1969056)
19 factorial$.ti,ab. (47513)
20 crossover$.ti,ab. (90695)
21 cross-over$.ti,ab. (37769)
22 placebo$.ti,ab. (366719)
23 (doubl$ adj blind$).ti,ab. (244461)
24 (singl$ adj blind$).ti,ab. (31632)
25 assign$.ti,ab. (490698)
26 allocat$.ti,ab. (202319)
27 volunteer$.ti,ab. (294793)
28 Crossover Procedure/ (75188)
29 double blind procedure/ (210186)
30 Randomized Controlled Trial/ (780977)
31 single blind procedure/ (51585)
32 controlled clinical trial/ (470843)
33 or/18-32 (3057119)
34 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (6803572)
35 33 not 34 (2727920)
36 17 and 35 (2416)
37 limit 36 to yr="2022 -Current" (1613)
38 (2022$ or 2023$).dd. (1098620)
39 36 and 38 (644)
40 37 or 39 (1718)
41 (conference abstract or "conference review").pt. (4886545)
42 40 not 41 (1285)
43 limit 42 to "remove preprint records" (1183)

PsycINFO
via Ovid http://ovidsp.ovid.com/
Date range: 1806 to August Week 4 2023
Date searched: 4th September 2023
Records retrieved: 273

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/ (25302)
2 coronavirus/ (5823)
3 syndromes/ (17602)
4 sequelae/ (3967)
5 1 or 2 (27701)
6 3 or 4 (21501)
7 5 and 6 (297)
8 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,id,ot. (205)
9 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,id,ot. (765)
10 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (38)
11 PASC.ti,ab,id,ot. (37)
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. (177)
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. (23)
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. (331)
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. (166)
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. (223)
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. (18)
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. (256)
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. (447)
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. (293)
22 or/8-21 (2330)
23 randomized clinical trials/ (487)
24 randomized controlled trials/ (1012)
25 clinical trials/ (12225)
26 clinical trial.md. (38416)
27 (randomi#ed or randomi#ation or randomi#ing).ti,ab,id. (109206)
28 randomly.ti,ab,id. (84020)

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. (128815)
30 (groups or (control* adj3 group*)).ab. (612731)
31 ((control* or trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw. (18954)
32 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id. (29247)
33 trial.ti. (38229)
34 (placebo or sham).ti,ab,id,hw. (58429)
35 treatment outcome.md. (23802)
36 treatment effectiveness evaluation/ (28413)
37 mental health program evaluation/ (2393)
38 or/23-37 (812333)
39 7 or 22 (2474)
40 38 and 39 (348)
41 limit 40 to yr="2022 -Current" (221)
42 (2022$ or 2023$).up. (311761)
43 40 and 42 (264)
44 41 or 43 (273)

CINAHL Ultimate
via Ebsco https://www.ebsco.com/
Date range: Inception to 20230904
Date searched: 4th September 2023
Records retrieved: 573

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") 904
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*) 1,286
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*) 1,563
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)) 328
S5 TI PASC OR AB PASC 100
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)) 555
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)) 265

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)) 721
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)) 1,002
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)) 896
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)) 51
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)) 95
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)) 1,053
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)) 4,037
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)) 903
S16 (MH "Randomized Controlled Trials") 139,970
S17 (MH "Double-Blind Studies") 54,543
S18 (MH "Single-Blind Studies") 16,109
S19 (MH "Random Assignment") 81,075
S20 (MH "Pretest-Posttest Design") 54,351
S21 (MH "Cluster Sample") 5,372
S22 TI randomised OR randomized 143,754
S23 AB random* 401,445
S24 TI trial 185,262
S25 MH (sample size) AND AB (assigned OR allocated OR control) 4,441
S26 MH (placebos) 14,192
S27 PT (randomized controlled trial) 152,737
S28 AB (control W5 group) 145,892
S29 MH (crossover design) OR MH (comparative studies) 485,564
S30 AB (cluster W3 RCT) 498
S31 MH animals+ 105,402
S32 MH (animal studies) 154,210
S33 TI (animal model*) 3,871
S34 S31 OR S32 OR S33 250,729

S35 MH (human) 2,730,049
S36 S34 NOT S35 216,429
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 1,031,187
S38 S37 NOT S36 983,127
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 10,512
S40 S38 AND S39 898
S41 S38 AND S39 Limiters - Published Date: 20220101-20230831 551
S42 (ZD 2022* or 2023*) 392,122
S43 S40 AND S42 301
S44 S41 OR S43 573

Appendix 2

The Joanna Briggs Institute Critical Appraisal Checklist for Randomized Controlled Trials

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

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

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

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

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

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

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

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

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

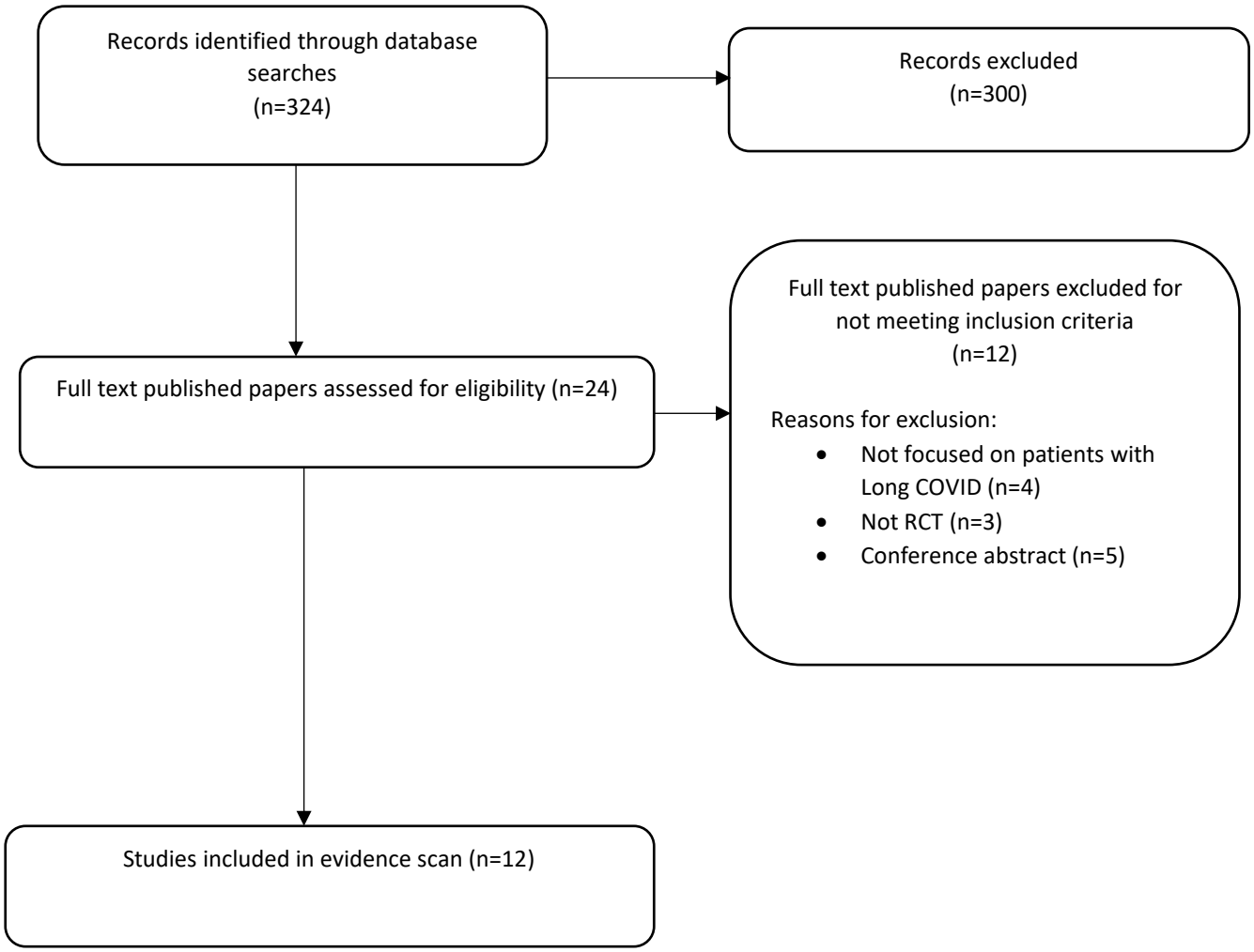
Q10 Were outcomes measured in the same way for treatment groups? Yes, No, Unclear, NA

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

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

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

Appendix 3: Flow of studies through the review



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

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

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

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

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Evidence for Policy and Practice Information Centre (EPPI Centre)
Social Science Research Unit, UCL Social Research Institute
UCL Institute of Education, University College London
18 Woburn Square
London WC1H 0NR

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Email: ioe.ssruadmin@ucl.ac.uk
Telephone: +44 (0)20 7331 5263