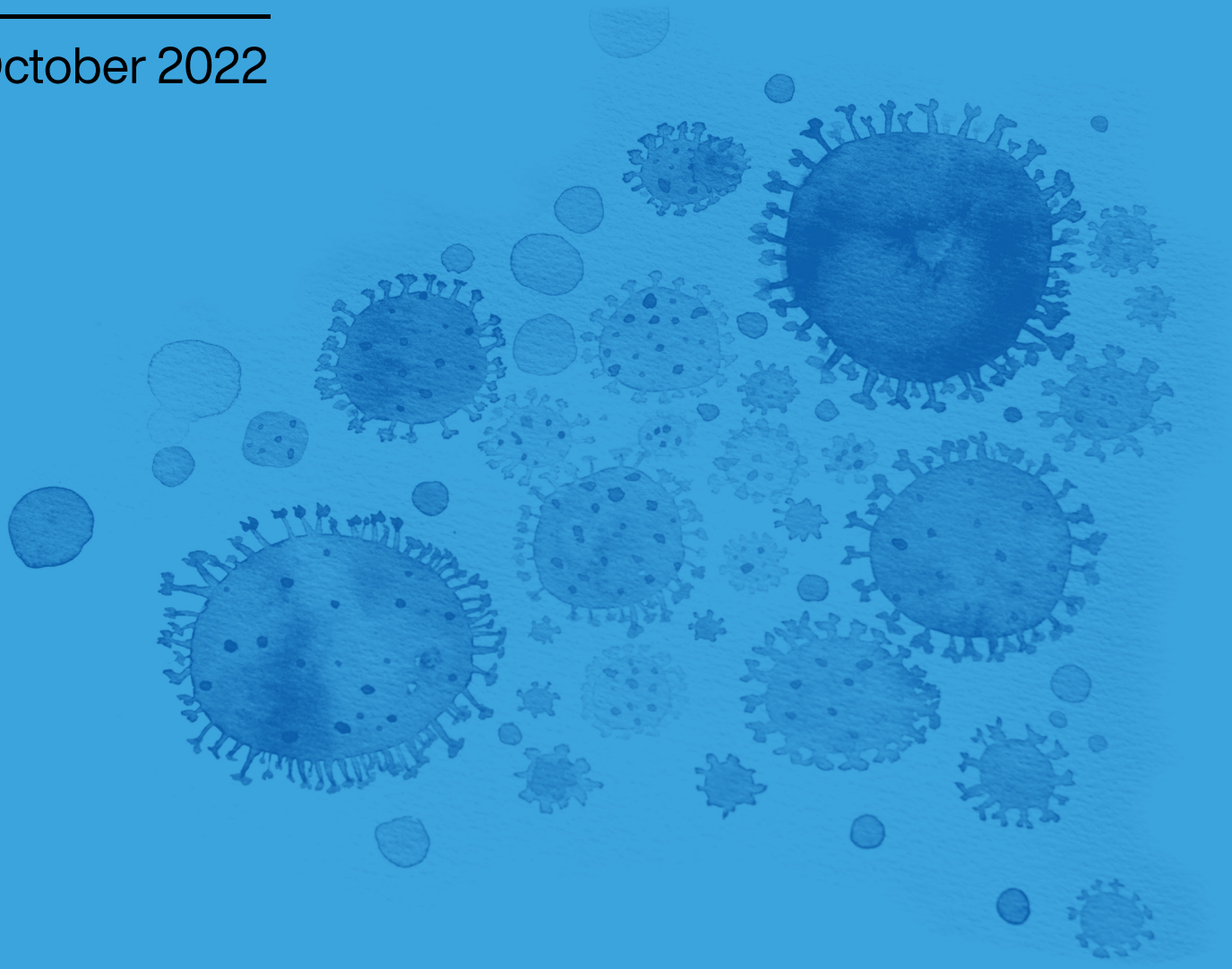
NIHR Policy Research Programme Reviews Facility

To support national policy development and implementation

Treatment and rehabilitation of Long COVID

A scope of the RCT literature: update

October 2022



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Treatment and rehabilitation of Long COVID: A scope of the literature. Update October 2022

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

October 2022

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Summary

- We identified 11 randomised controlled trials published since June 2022 that were focused on Long COVID treatment or rehabilitation. Across two reports, we have now identified and assessed 25 trials published in 2022.
- A majority of trials focused on evaluating treatments for people with persistent problems with their sense of smell (olfactory dysfunction).
- Trial quality varied and inadequate reporting of methods often prevented a full assessment of the risk of bias. However, six trials were rated positively for at least 11 out of the 13 criteria that we assessed.

Introduction

This is the second 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 2022.

Method

Identification of studies

We searched 5 databases to identify relevant studies for this update:

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 infection. The original search strategy was reviewed and updated by an information specialist. 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.

As we updated and expanded our search strategy, we extended the time frame covered by the latest searches back to January 2022 to identify any studies added to the databases or published up to June that had not been included in our first report. [(1)] No additional studies were identified and therefore the trials included in the current report were all published between June and September 2022. No language restrictions were applied to the searches. 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.

Full search strategies for CENTRAL, MEDLINE, Embase, PsycINFO and CINAHL can be found in Appendix 1 (page 11).

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. [2]

Publication type and status - any publication type reporting the findings from a RCT (e.g. full papers, research letters etc).

Quality assessment

Each study was appraised according to the Joanna Briggs Institute (JBI) Checklist for Randomized Controlled Trials. [3] In contrast to the Cochrane Risk of Bias Tool, [4] the JBI checklist does not require an assessment of bias for specific outcomes. It provides instead a general appraisal of each trial as a whole, which was needed in this piece of work as we were not seeking to extract and synthesise 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 19).

Key findings

We screened 1009 records and identified 11 RCTs that had been published since the beginning of June 2022. [5-15] This is slightly fewer than the 14 trials we identified in our previous report in July, but that included papers published over a longer period. The flow of studies through the current update is shown in Appendix 3 (page 20). Table 1 (page 4) presents the aim(s) and key characteristics of the 11 trials.

Interventions

Seven out of the 11 RCTs focused primarily on people with persistent problems with their sense of smell (olfactory dysfunction) and investigated the effectiveness of various nasal sprays, rinses, oral supplements and/or olfactory training as potential treatments. [5, 6, 9-12, 14] One RCT evaluated hyperbaric oxygen therapy as a treatment for multiple Long COVID symptoms including smell, taste, sleep or cognitive dysfunction; joint and muscle aches; anxiety and sadness; and fatigue. [15] Another trial had the primary objective of assessing the feasibility and safety of vagus nerve stimulation for treating nine persistent neuropsychiatric symptoms (anxiety, depression, vertigo, anosmia, ageusia, headaches, fatigue, irritability and brain fog). [7] Two trials examined the effectiveness of oral supplements [8] and a telerehabilitation programme [13] for restoring respiratory function/physical fitness. The trials included in our July report tended to focus on physical therapy and general/multiple symptoms of Long COVID. Only one study had a primary focus on olfactory dysfunction.

Participants

Three trials recruited participants who had experienced persistent effects for at least four weeks after the onset of COVID symptoms or diagnosis. [11,12,14] In the remaining eight trials, participants were recruited up to 12 months after recovery or hospital discharge [5,6, 8,9, 13] or at least three months after diagnosis/positive test. [7, 10, 15]

Countries

Two of the 11 trials were conducted in Egypt; [5, 6] and two in the USA. [7, 10] The remaining seven trials were conducted in Brazil; [14] China; [13] Iran; [11] Israel; [15] Italy; [9] Poland; [8] and the UK. [12]

Trial quality

Assessments of the trials against the JBI criteria are provided in Table 2 (pages 7 and 8). Only one trial was assessed as having a low risk of bias for all 13 appraisal criteria. [10] We rated three trials positively for 12 out of the 13 criteria. [5, 6, 11] and two other trials met at least 11 criteria. [13, 15]

In two of the trials, it was unclear if the sample size was sufficient for an accurate analysis. [5, 6] In the trial by Hosseinpoor et al., we could not tell if an Intention to Treat (ITT) analysis had been conducted. [11] This form of analysis is generally recommended to minimise bias and is considered an indicator of good methodological quality. [3] The trial reported by Zilberman-Itskovich et al. did not use an ITT analysis and it was unclear if there was blinding of the trial personnel who delivered the treatment.[15] In the trial by Li et al., participants knew whether they were in the intervention or comparator group, and the trial personnel responsible for delivering the treatment were also aware of patients' group allocation. [13]

The remaining five trials gained positive ratings for between three and seven criteria. [7-9, 12, 14] Inadequate reporting of key information was an issue with these trials, which meant we could not determine the risk of bias across multiple domains. For example, in four out of the five trials, we could not tell if an appropriate procedure had been used to prevent researchers from knowing whether the next patient would be allocated to the treatment or comparator group (Q2); [7, 9, 12, 14] or whether researchers had used an appropriate method of randomisation for allocating participants to treatment groups (Q1). [7, 9, 12, 14] It was also not possible to tell whether the trial personnel who assessed the outcomes of interest were blinded to participants' group allocation in four of the studies (Q6). [8, 9, 12, 14]

Only one of the five trials received a positive rating for all three criteria relating to the blinding of study participants and trial personnel (Q4, Q5, Q6). [7] In three of the five studies, there was no blinding of either trial participants or the personnel who administered the treatment. [8, 9, 12] In one trial, we could not tell if participants and/or the personnel who administered the treatment were blinded or not, but it was considered unlikely owing to the nature of the intervention. [14]

To conclude, this second evidence scan identified 11 RCTs published since June 2022 that examined interventions for the treatment or rehabilitation of people with Long COVID. Across our two reviews, we have now identified and assessed 25 trials published in 2022. A majority of trials (n=7) in the current update focused on evaluating treatments for persistent olfactory dysfunction. Trial quality varied and inadequate reporting of methods frequently precluded a full assessment of the risk of bias. However, six trials were rated positively for at least 11 out the 13 criteria that we assessed.

Table 1: Study characteristics (n=11)

First author Country	Aim of study	Main symptom or effect experienced	Post COVID time	Participants' gender (n) and % female	Primary outcome of interest	Comparator
Abdelazim [5] Egypt	To investigate the use of intranasal tetra sodium pyrophosphate for improving olfactory disorders after COVID-19	Olfactory dysfunction	After recovery: more than 90 days after two negative SARS-CoV-2 tests	Mixed (64) 59% female	Olfactory function	Intranasal spray of sodium chloride
Abdelazim [6] Egypt	To evaluate the impact of intranasal sodium gluconate to improve the sense of smell in patients with olfactory dysfunction after COVID-19	Olfactory dysfunction	After recovery: more than 90 days after two negative SARS-CoV-2 tests	Mixed (50) 62% female	Olfactory function	Intranasal spray of sodium chlorine
Badran [7] USA	To investigate whether self-administered, remote-monitored transcutaneous auricular vagus nerve stimulation was feasible, tolerable, and reduced symptoms associated with Long COVID	Neuropsychiatric symptoms (anxiety, depression, vertigo, anosmia, ageusia, headaches, fatigue, irritability, brain fog)	After positive test: The mean time from confirmed COVID-19 test to enrolment was 7.1 ± 2.75 months (min: 3 months, max: 11 months)	Mixed (12) 62% female (8/13) unclear if the drop-out before randomisation was male or female	Feasibility, tolerability and/or safety: Assistance required; heart rate; compliance; and adverse effects	Sham stimulation
Chudzik [8] Poland	To investigate whether 1-Methylnicotinamide (1-MNA) supplements could improve exercise tolerance and decrease fatigue	Respiratory function/physical fitness (limited exercise tolerance) Fatigue/lack of energy	After recovery: symptoms continued for at least four weeks since the last	Mixed (50) 68% female	Physical fitness: Improvement in exercise performance	No supplementation

	among patients recovering from SARS-CoV-2		symptoms of infection			
De Luca* [9] Italy	To investigate whether treatment with Palmitoylethanolamide and luteolin (PEA-LUT), with or without olfactory training, was associated with an improvement in measures of olfactory function and mental clouding in patients affected by Long COVID	Olfactory dysfunction	After recovery: 180 days (6 months) after negative COVID-19 test	Mixed (69) 62% female	Olfactory function	No olfactory training
Gupta [10] USA	To evaluate the efficacy and safety of theophylline added to saline nasal irrigation compared with placebo for COVID-19 related olfactory dysfunction	Olfactory dysfunction	After diagnosis: symptoms persisting for 3 to 12 months following suspected COVID-19 infection	Mixed (51) 71% female	Olfactory function	Saline nasal irrigation with placebo (lactose)
Hosseinpoor [11] Iran	To assess the effect of mometasone furoate intranasal spray on the improvement of smell dysfunction in post-COVID-19 patients	Olfactory dysfunction	After diagnosis: a definitive diagnosis of COVID-19 and persistent olfactory dysfunction between 30 to 90 days	Mixed (80) Randomised: 56% female (45/80) Analysed: 64% female (45/70)	Olfactory function	Placebo (sodium chloride intranasal spray)

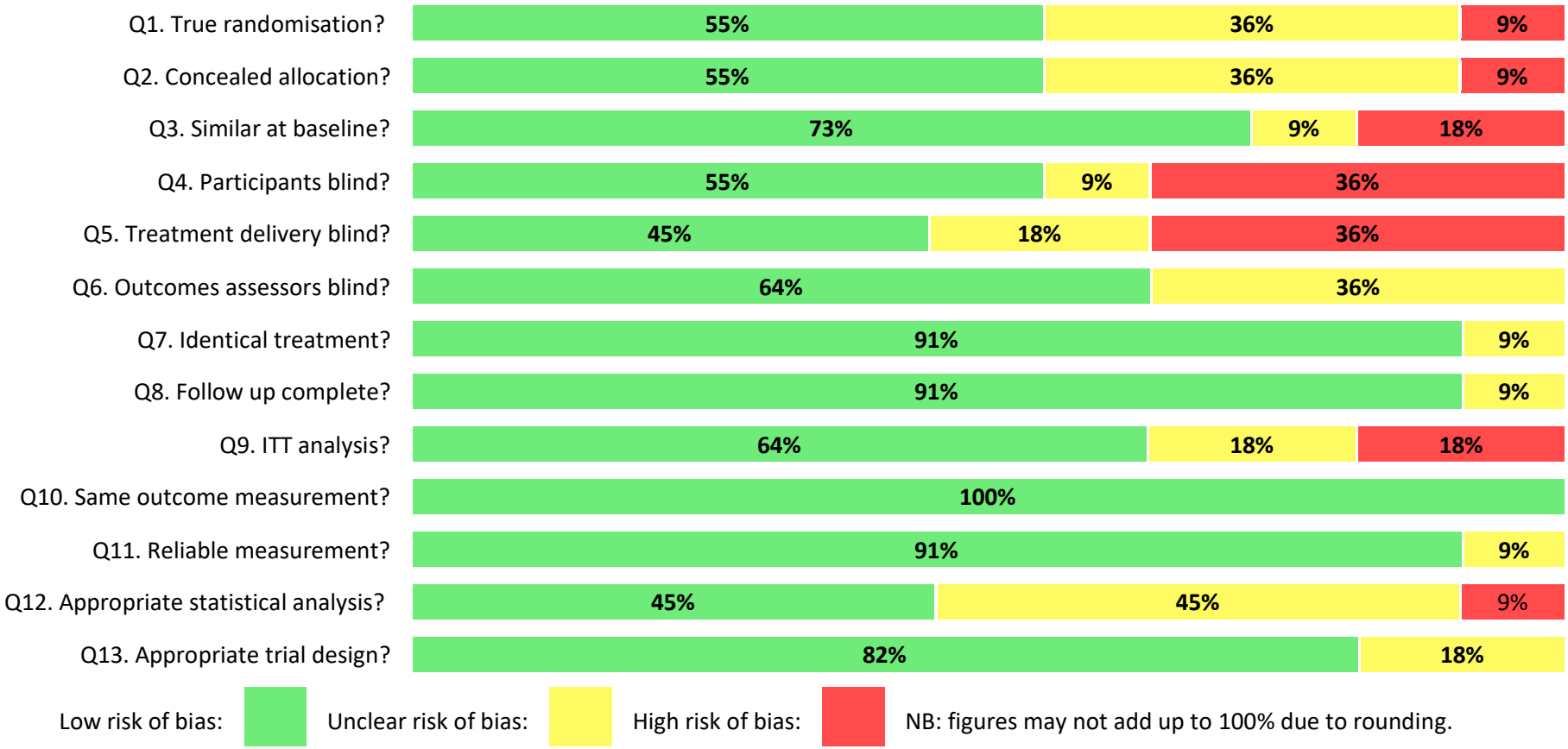
Lechner [12] UK	To evaluate the efficacy of early olfactory training for COVID-19 olfactory dysfunction	Olfactory dysfunction	After symptom onset: persisting symptoms for at least 4 weeks	Mixed (63) (51 completed) 89% female (55/62)	Olfactory function	Control - safety information
Li [13] China	To investigate the efficacy of a telerehabilitation programme for COVID-19 (TERECO) compared with no rehabilitation	Respiratory function/physical fitness (persistent dyspnoea)	From hospital discharge: Mean time to baseline assessment was 70 days	Mixed (120) 55% female	Physical fitness: Functional exercise capacity	Short educational instructions at baseline
Pires [14] Brazil	To assess whether olfactory training performance can be optimised using eight fragrances (rose, eucalyptus, clove, lemon, citronella, mint, vanilla, and cedar wood) over a shorter period in patients with persistent olfactory dysfunction after COVID-19	Olfactory dysfunction	After symptom onset: at least 4 weeks after the onset of COVID-19 symptoms	Mixed (80) 65% female	Olfactory function	Classical olfactory training with 4 essential oils: rose, eucalyptus, clove, and lemon
Zilberman-Itskovich [15] Israel	To evaluate the effects of hyperbaric oxygen therapy on patients suffering from post-COVID-19 condition	General/multiple symptoms including sleep, smell, and taste dysfunction; cognitive dysfunction; joint and muscle aches; anxiety and sadness; and fatigue	After positive test: more than three months following a positive RT-PCR test	Mixed (79 randomised; 73 completed) Completed: 60% female (44/73)	Cognitive function: Global Cognitive Score, including memory, executive function, attention, information processing speed, and motor skills	Sham control

*The research by De Luca et al. was a trial extension, which the authors described as a longitudinal study. It met the criteria for inclusion in the current report.

Table 2: JBI risk of bias assessment

First author (publication year)	Q1. True randomisation?	Q2. Concealed allocation?	Q3. Similar at baseline?	Q4. Participants blind?	Q5. Treatment delivery blind?	Q6. Outcomes assessors blind?	Q7. Identical treatment?	Q8. Follow up complete?	Q9. ITT analysis?	Q10. Same outcome measurement?	Q11. Reliable measurement?	Q12. Appropriate statistical analysis?	Q13. Appropriate trial design?
Abdelazim (2022)	+	+	+	+	+	+	+	+	+	+	+	?	+
Abdelazim (2022)	+	+	+	+	+	+	+	+	+	+	+	?	+
Badran (2022)	?	?	-	+	+	+	+	+	+	+	?	?*	?
Chudzik (2022)	-	-	+	-	-	?	?	+	+	+	+	+	+
De Luca (2022)	?	?	-	-	-	?	+	?	?	+	+	?	?
Gupta (2022)	+	+	+	+	+	+	+	+	+	+	+	+	+
Hosseinpoor (2022)	+	+	+	+	+	+	+	+	?	+	+	+	+
Lechner (2022)	?	?	?	-	-	?	+	+	-	+	+	-	+
Li (2022)	+	+	+	-	-	+	+	+	+	+	+	+	+
Pires (2022)	?	?	+	?	?	?	+	+	+	+	+	?	+
Zilberman-Itskovich (2022)	+	+	+	+	?	+	+	+	-	+	+	+	+

*The study was not powered to examine clinical effectiveness as it was a secondary objective. No inferential findings related to effectiveness were reported.
+ = low risk of bias; - = high risk of bias; and ? = unclear risk of bias


Q1. True randomisation?
55%
36%
9%
Q2. Concealed allocation?
55%
36%
9%
Q3. Similar at baseline?
73%
9%
18%
Q4. Participants blind?
55%
9%
36%
Q5. Treatment delivery blind?
45%
18%
36%
Q6. Outcomes assessors blind?
64%
36%
Q7. Identical treatment?
91%
9%
Q8. Follow up complete?
91%
9%
Q9. ITT analysis?
64%
18%
18%
Q10. Same outcome measurement?
100%
Q11. Reliable measurement?
91%
9%
Q12. Appropriate statistical analysis?
45%
45%
9%
Q13. Appropriate trial design?
82%
18%
Low risk of bias:
Unclear risk of bias:
High risk of bias:
NB: figures may not add up to 100% due to rounding.

References

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Appendix 1 – search strategies

Cochrane Controlled Register of Trials (CENTRAL)
via Wiley http://onlinelibrary.wiley.com/
Issue: Issue 9 of 12, September 2022
Date searched: 15th September 2022
Records retrieved: 514

Although 514 records were identified overall in CENTRAL, trial register records were removed from this set, leaving a total of 358 records downloaded for this update.

#1 MeSH descriptor: [COVID-19] this term only and with qualifier(s): [complications - CO] 106
#2 MeSH descriptor: [COVID-19] this term only 2207
#3 MeSH descriptor: [SARS-CoV-2] this term only 1094
#4 MeSH descriptor: [Syndrome] this term only 5548
#5 MeSH descriptor: [Survivors] this term only 1279
#6 #2 or #3 2212
#7 #4 or #5 6826
#8 #6 and #7 23
#9 #1 or #8 129
#10 (long next (covid* or covid-19 or covid19 or coronavirus) or longcovid*):ti,ab,kw 111
#11 (post next (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2) or postcovid*):ti,ab,kw 306
#12 ((post acute or postacute) near/2 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 610
#13 PASC:ti,ab,kw 24
#14 (sequela* near/6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 76
#15 (chronic near/2 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 19
#16 (ongoing next (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 70
#17 ((long* term or longterm) near/3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 422
#18 (persist* near/6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 120
#19 ((post discharg* or postdischarg*) near/4 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 535
#20 ((long haul* or longhaul*) near/6 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 235
#21 (surviv* near/3 (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 126
#22 (after next (covid* or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)):ti,ab,kw 148
#23 ((ongoing or lasting or prolonged or fluctuat* or residual* or continu* or linger*) near/6 (symptom* or effect* or complication* or sequela* or syndrome or illness* or 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 82
#24 {OR #10-#23} 1500
#25 #9 or #24 with Cochrane Library publication date Between Jan 2022 and Dec 2022, in Trials 506
#26 #9 or #24 with Publication Year from 2022 to 2022, in Trials 405

#27 #25 or #26 514

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 13, 2022
Date searched: 15th September 2022
Records retrieved: 332

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

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

1 post-acute COVID-19 syndrome.mp. (1280)
2 COVID-19 post-intensive care syndrome.mp. (5)
3 COVID-19/co [Complications] (11663)
4 COVID-19/ or SARS-CoV-2/ (188610)
5 Syndrome/ (121149)
6 Survivors/ (29001)
7 5 or 6 (150037)
8 4 and 7 (757)
9 1 or 2 or 3 or 8 (12320)
10 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,kf,ot,bt. (1831)
11 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,kf,ot,bt. (5149)
12 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kf,ot,bt. (454)
13 PASC.ti,ab,kf,ot,bt. (434)
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. (1496)
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. (216)
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. (2657)
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. (1376)
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. (2569)
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. (61)
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. (186)
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. (2136)

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. (5642)
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 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. (1831)
24 or/10-23 (20445)
25 9 or 24 (29896)
26 randomized controlled trial.pt. (577088)
27 controlled clinical trial.pt. (95028)
28 randomi#ed.ab. (687958)
29 placebo.ab. (231706)
30 clinical trials as topic.sh. (200377)
31 randomly.ab. (391319)
32 trial.ti. (270361)
33 26 or 27 or 28 or 29 or 30 or 31 or 32 (1516458)
34 exp animals/ not humans.sh. (5046262)
35 33 not 34 (1397172)
36 25 and 35 (845)
37 limit 36 to yr="2022 -Current" (326)
38 2022*.dt. (1136867)
39 36 and 38 (289)
40 37 or 39 (332)

Embase
via Ovid http://ovidsp.ovid.com/
Date range: 1974 to 2022 September 14
Date searched: 15th September 2022
Records retrieved: 540

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/ (2161)
2 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,kw,ot. (1739)
3 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,kw,ot. (6374)
4 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,kw,ot. (439)
5 PASC.ti,ab,kw,ot. (512)
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. (1811)
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. (254)
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. (2613)
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. (1630)

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. (3113)
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. (102)
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. (194)
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. (2935)
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. (7131)
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 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. (2148)
16 or/2-15 (24353)
17 1 or 16 (24570)
18 random$.ti,ab. (1833625)
19 factorial$.ti,ab. (44694)
20 crossover$.ti,ab. (85874)
21 cross-over$.ti,ab. (36035)
22 placebo$.ti,ab. (348573)
23 (doubl$ adj blind$).ti,ab. (233740)
24 (singl$ adj blind$).ti,ab. (29519)
25 assign$.ti,ab. (460355)
26 allocat$.ti,ab. (186854)
27 volunteer$.ti,ab. (283398)
28 Crossover Procedure/ (71425)
29 double blind procedure/ (198668)
30 Randomized Controlled Trial/ (727689)
31 single blind procedure/ (47513)
32 controlled clinical trial/ (467065)
33 or/18-32 (2872431)
34 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (6535606)
35 33 not 34 (2562344)
36 17 and 35 (1432)
37 limit 36 to yr="2022 -Current" (643)
38 2022$.dd. (650914)
39 36 and 38 (367)
40 37 or 39 (733)
41 (conference abstract or "conference review").pt. (4547656)
42 40 not 41 (540)

PsycINFO
via Ovid http://ovidsp.ovid.com/
Date range: 1806 to September Week 1 2022
Date searched: 21st September 2022
Records retrieved: 95

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/ (12561)
2 coronavirus/ (4617)
3 syndromes/ (16683)
4 sequelae/ (3851)
5 1 or 2 (14620)
6 3 or 4 (20473)
7 5 and 6 (187)
8 ((long adj (covid$ or covid-19 or covid19 or coronavirus)) or longcovid$).ti,ab,id,ot. (68)
9 ((post adj (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)) or postcovid$).ti,ab,id,ot. (371)
10 ((post acute or postacute) adj2 (covid$ or covid-19 or covid19 or coronavirus or SARS-CoV-2 or SARS-CoV2 or SARSCoV2 or SARSCoV-2)).ti,ab,id,ot. (11)
11 PASC.ti,ab,id,ot. (21)
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. (106)
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. (9)
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. (210)
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. (97)
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. (112)
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. (9)
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. (148)
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. (260)
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 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. (143)
22 or/8-21 (1304)
23 randomized clinical trials/ (374)
24 randomized controlled trials/ (906)
25 clinical trials/ (12100)
26 clinical trial.md. (34615)
27 (randomi#ed or randomi#ation or randomi#ing).ti,ab,id. (102223)
28 randomly.ti,ab,id. (80626)
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. (121476)
30 (groups or (control* adj3 group*)).ab. (588618)
31 ((control* or trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw. (17717)
32 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id. (28400)

33 trial.ti. (35865)
34 (placebo or sham).ti,ab,id,hw. (56628)
35 treatment outcome.md. (22834)
36 treatment effectiveness evaluation/ (27037)
37 mental health program evaluation/ (2291)
38 or/23-37 (778792)
39 7 or 22 (1416)
40 38 and 39 (173)
41 limit 40 to yr="2022 -Current" (74)
42 2022$.up. (131466)
43 40 and 42 (89)
44 41 or 43 (95)

CINAHL Plus
via Ebsco https://www.ebsco.com/
Date range: Inception to 20220915
Date searched: 15th September 2022
Records retrieved: 237

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") 371

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*) 726

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*) 1,006

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)) 200

S5 TI PASC OR AB PASC 68

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)) 364

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)) 197

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)) 591

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)) 744

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)) 647

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)) 36

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)) 75

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)) 797

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)) 2,822

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 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 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)) 652

S16 (MH "Randomized Controlled Trials") 132,927

S17 (MH "Double-Blind Studies") 53,616

S18 (MH "Single-Blind Studies") 15,730

S19 (MH "Random Assignment") 75,619

S20 (MH "Pretest-Posttest Design") 50,428

S21 (MH "Cluster Sample") 5,063

S22 TI randomised OR randomized 131,444

S23 AB random* 383,083

S24 TI trial 169,625

S25 MH (sample size) AND AB (assigned OR allocated OR control) 4,374

S26 MH (placebos) 13,801

S27 PT (randomized controlled trial) 146,156

S28 AB (control W5 group) 137,789

S29 MH (crossover design) OR MH (comparative studies) 466,917

S30 AB (cluster W3 RCT) 471

S31 MH animals+ 104,056

S32 MH (animal studies) 149,010

S33 TI (animal model*) 3,636

S34 S31 OR S32 OR S33 244,226

S35 MH (human) 2,601,634

S36 S34 NOT S35 210,561

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 980,487

S38 S37 NOT S36 933,955

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 7,332

S40 S38 AND S39 558

S41 S38 AND S39 Limiters - Published Date: 20220101-20221231 217

S42 (ZD 2022*) 273,962

S43 S40 AND S42 194

S44 S41 OR S43 237

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

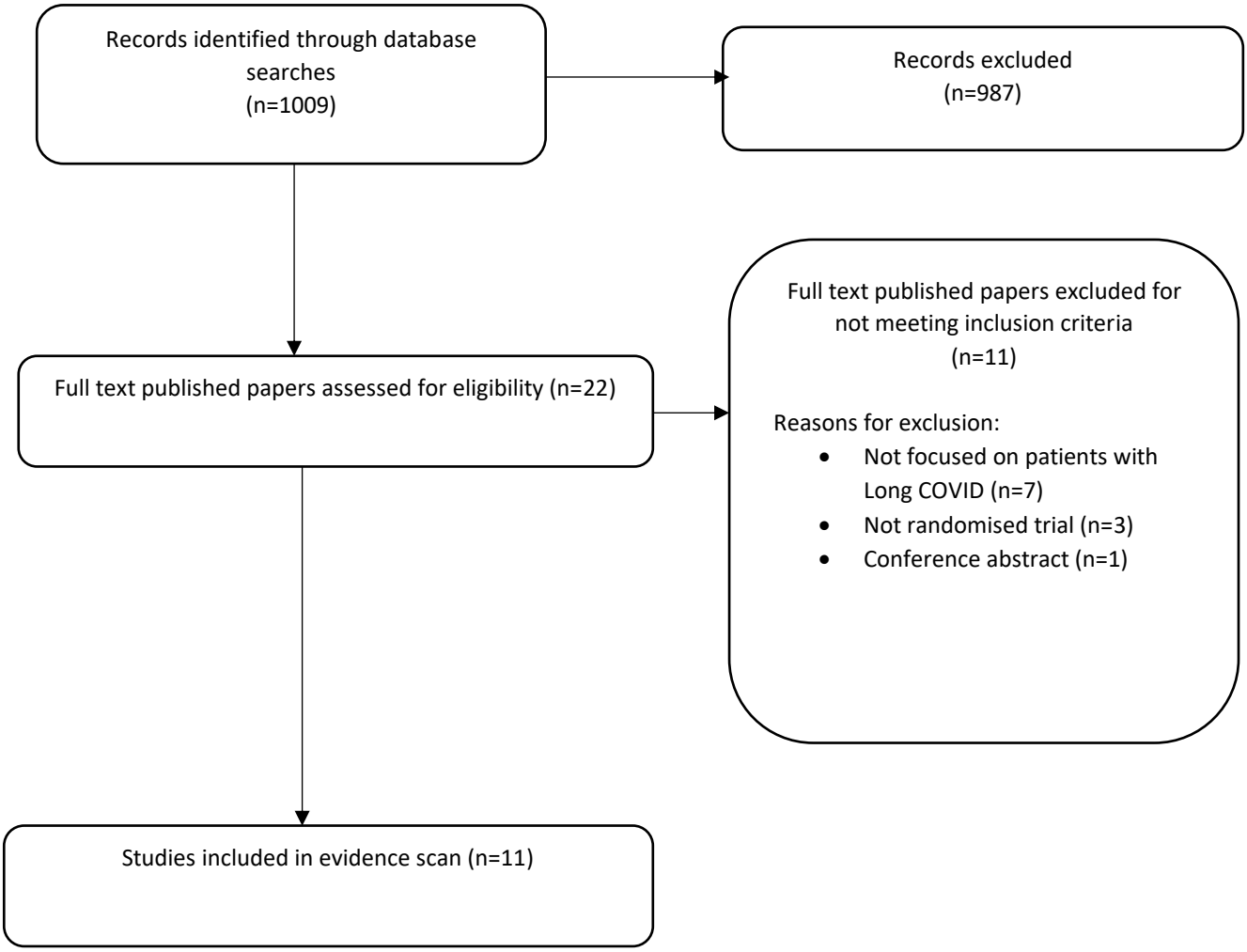
Q10 Were outcomes measured in the same way for treatment groups? Yes, No, Unclear, NA

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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- 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.ssru@ucl.ac.uk
Telephone: +44 (0)20 7331 5263