

BMJ Open Protocol for a systematic review of interventions targeting mental health, cognition or psychological well-being among individuals with long COVID

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ABSTRACT

Introduction For some people, COVID-19 infection leads to negative health impacts that can last into the medium or long term. The long-term sequelae of COVID-19 infection, or 'long COVID', negatively affects not only physical health, but also mental health, cognition or psychological well-being. Complex, integrated interventions are recommended for long COVID, including psychological components; however, the effectiveness of such interventions has yet to be critically evaluated. This protocol describes a systematic review to be conducted of scientific literature reporting on clinical trials of interventions to promote mental health, cognition or psychological well-being among individuals with long COVID.

Methods and analysis The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines will be followed. A health sciences librarian will identify the relevant literature through comprehensive systematic searches of Medline, Embase, APA PsycINFO, Cumulative Index to Nursing and Allied Health Literature, medRxiv, PsyArXiv, China National Knowledge Internet and WANFANG Data databases, as well as The Cochrane Central Register of Controlled Trials, clinicaltrials.gov and the WHO International Clinical Trials Registry Platform. Studies will be selected through a title and abstract review, followed by a full-text review using inclusion and exclusion criteria. Data extracted will include intervention descriptions and efficacy metrics. Data will be narratively synthesised; if the data allow, a meta-analysis will be conducted. Risk of bias assessment will be conducted using the Cochrane Risk of Bias 2.0 tool.

Ethics and dissemination Ethical approval for systematic reviews is not required. As researchers and clinicians respond to the new clinical entity that long COVID represents, this review will synthesise a rapidly emerging evidence base describing and testing interventions to promote mental health, cognition or psychological well-being. Results will therefore be disseminated through an open-access peer-reviewed publication and conference presentations to inform research and clinical practice.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ With broad inclusion criteria, all relevant clinical trials will be included.
- ⇒ Data synthesis may be narrative, as meta-analytical synthesis will only be possible if the nature of the literature permits.
- ⇒ Study quality and risk of bias will be assessed using multiple standardised metrics.
- ⇒ Search terms and the data extraction plan will need to be refined iteratively as the literature emerges.

INTRODUCTION

Prolonged symptoms after COVID-19 infection constitute a considerable medical concern in the ongoing COVID-19 pandemic. Most people who acquire a COVID-19 infection experience short-term illness, with recovery within days or weeks.¹ However, some people experience symptoms months after the acute infection period.² This clinical entity, which was first identified by patients themselves, has been given a number of names, including long COVID, post-COVID syndrome and COVID-19 long haulers.³ Symptoms commonly observed in long COVID include fatigue, headaches, difficulty concentrating, shortness of breath, dizziness, myalgia, insomnia, depression and anxiety, as part of a mixed constellation of multisystem symptoms with an unknown duration.^{4 5} A meta-analysis suggests that 43% of people who contract COVID-19 are reporting long-term symptoms consistent with long COVID.⁶ By conservative estimates in the context of limited testing capacity, 500 million people worldwide had been infected by COVID-19 in mid-April 2022⁷; at a rate of 43% experiencing long-term symptoms, hundreds of millions of people around the



world have experienced or will experience some degree of long COVID.

A number of risk factors for long COVID have been identified, including older age, female sex, a higher body mass index, comorbidities and more severe COVID-19 symptoms.^{8,9} However, anyone can develop long COVID, from young people with no pre-existing conditions to older adults and those with a complex health status.¹⁰ Social isolation, decreased physical activity, changed lifestyles and pandemic-related social and economic insecurity may contribute to developing the physical and psychological symptoms of long COVID.⁸ For some people, long COVID may become a long-term, debilitating, multisystemic disability.^{11,12}

The COVID-19 pandemic has had substantial mental health repercussions,¹³ as the public health restrictions put into place to reduce the spread of the virus have disrupted many of the protective factors¹⁴⁻¹⁶ that support mental health and wellness. In addition to these widespread mental health impacts from the pandemic, long COVID is specifically associated with mental health impacts. People with long COVID are presenting with anxiety, depression and post-traumatic stress disorder, as well as neurocognitive issues³ and other multisystemic symptoms that impair functioning, well-being and quality of life.¹⁷ Indeed, individuals with long COVID can experience both the mental health symptoms specific to long COVID and those associated with the pandemic's impacts on societies at large.¹⁸

The National Institute for Health and Care Excellence (NICE) has issued clinical practice guidelines for the treatment for long COVID.¹⁹ According to NICE, treatment requires integrated, multidisciplinary models of care that bring patients together with healthcare practitioners from across specialties to meet the wide range of long-term needs with which patients present. In addition to treatments for physical symptoms, NICE guidelines highlight the importance of attending to mental health, cognition and well-being, including among individuals with pre-existing or newly emerging mental health problems. It is therefore important that we embed evidence-based interventions to promote mental and cognitive health and psychological well-being into long COVID care.

Integrated, multicomponent interventions that are applied to heterogeneous populations in heterogeneous treatment settings can be considered 'complex' interventions according to the UK Medical Research Council complex intervention framework.²⁰ The recommended type of integrated care for long COVID would be expected to consist of multiple evidence-based components, yet be tailored to the individual patient to produce a range of possible outcomes, while being delivered by a variety of care providers across disciplines.¹⁹ Such complex interventions require careful preparation, implementation and evaluation to ensure efficacy and effectiveness.

Our team's systematic review of registered trials of interventions for mental health, cognition or psychological

well-being in long COVID revealed that the research on such interventions is only just beginning to emerge.²¹ Given that COVID-19 research has been emerging at an extremely rapid pace,²² the associated long COVID treatment literature is expected to follow suit. Timely reviews of the literature on this topic will therefore be key to the process of developing and optimising the recommended complex, integrated interventions for individuals with long COVID.²³

Objectives

This paper describes the protocol for a systematic review of clinical trials testing interventions to promote mental health, cognition or psychological well-being among individuals with long COVID.

METHODS AND ANALYSIS

Reporting guidelines

This systematic review protocol follows the protocol version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (ie, PRISMA-P).²⁴ The systematic review will follow the PRISMA guidelines.²⁵

Research question

This systematic review will synthesise the scientific literature on interventions that have been tested for mental health, cognition or psychological well-being among individuals experiencing long COVID. Specific research questions are: (1) what are the outcomes of interventions that have been tested for mental health, cognition or psychological well-being among individuals with long COVID? (2) What is the design and quality of the trials?

Eligibility criteria

This review will include articles reporting the results of clinical trials of any intervention aiming to promote mental health, cognition or psychological well-being among people who have long COVID, as described in [table 1](#). Based on our existing review of registered trials on this topic,²¹ the literature is expected to report on psychological interventions, pharmacological interventions, nutritional or natural supplement interventions, cognitive and neurorehabilitation interventions and physiotherapy or physical rehabilitation. Applying the inclusion criteria, we will include these types of interventions in the review, as well as any other types of interventions that may emerge.

To be included, articles must report on the outcomes of an intervention aiming to promote mental health, cognition or psychological well-being in patients with long COVID symptoms after a confirmed or suspected COVID-19 infection. Controlled and uncontrolled clinical trials will be included. Articles can originate from any country and can report on participants of any age group or other sociodemographic characteristic. To capture the broadest range of studies, the article's definition of long COVID will be accepted, provided that it

Table 1 Trials to be included in the review

| Eligible studies | |
|------------------|---|
| Populations | Patients with long COVID symptoms at least 4 weeks after confirmed or suspected COVID-19 infection Any country, any sociodemographic characteristics |
| Interventions | Interventions aiming to promote mental health, cognition or psychological well-being |
| Comparators | With any comparison group Without a comparison group |
| Outcomes | Impact on variables specific to mental health, cognition or psychological well-being |

reports on symptoms experienced at least 4 weeks after acute infection, consistent with the observed lower limit of duration observed in currently registered trials.²¹ Articles can be published in print, online ahead of print or in unreviewed preprint format; unpublished summaries of findings will also be accepted. For articles published in a language other than English or French, we will contact authors for English-language summaries; if unavailable, we will have the abstracts translated and will include the English-language abstracts in the review. Excluded will be any trials of participants who did not have long COVID, trials conducted prior to 2020 (ie, before the COVID-19 pandemic), animal trials, treatment guidelines and opinion papers.

Information sources

A comprehensive search will be conducted in Medline, Embase, APA PsycINFO, Cumulative Index to Nursing and Allied Health Literature, medRxiv, PsyArXiv, China National Knowledge Internet and WANFANG Data databases, as well as The Cochrane Central Register of Controlled Trials, clinicaltrials.gov and the WHO International Clinical Trials Registry Platform using the search strategy described below. Reference lists of included articles and any identified review articles will also be examined.

Search strategy

The tentative search strategy has been developed by a health sciences librarian (table 2). Given the paucity of literature on this topic to date, the search strategy may be refined by the librarian at the time of the review when literature is available. It will therefore be tested and iteratively refined and optimised as the literature emerges. Search concepts built using database-specific subject headings, natural language keywords and advanced search operators will focus on (1) mental health, cognition and psychological well-being, (2) clinical trials, built using an established clinical trials filter²⁶ and (3) long COVID search components using an established and tested shared search strategy.²⁷ No geographical or language limits will be placed on the search, but it will be limited to a timeline of 2020 to present. The English search strategy will be translated to Chinese for use in Chinese searches and the Chinese search strategy will be optimised to each relevant database by qualified Chinese-speaking team members. In addition, specific title and author searches

will be conducted for all studies identified in our existing systematic review of registered trials;²¹ if unpublished, lead researchers for each previously identified trial will be contacted to request any results that might be eligible for inclusion. On completion of the article selection process, the search will be rerun to update the findings.

Study selection

Identified records will be uploaded into Covidence systematic review software²⁸ for record management. Titles and abstracts will be reviewed independently by two study staff based on the inclusion and exclusion criteria; any conflicts will be resolved by consensus through discussion with the project lead. Selected documents will be reviewed at the full-text level by two staff in the same manner until a final set of included articles is obtained. The record review and selection process will be illustrated using a PRISMA flow chart.²⁵

Data extraction

The documents selected for inclusion will undergo data extraction and analysis. Data will be extracted as a team by the two study staff and research lead together for the first five documents as a pilot and training stage, to establish consensus. The remaining data will be extracted by one of the study staff and confirmed by a second team member, in discussion with the study lead for any uncertainties. Data extraction will tentatively include the elements summarised in table 3. Additional elements may be identified over the course of the project as literature emerges, in an iterative manner.

Outcomes and prioritisation

Given the rapidly emerging nature of this new literature base, it is intended that all intervention outcomes specific to the mental health, cognition or psychological well-being of research participants will be sought, including pre-assessment and post-assessments, with follow-up measures where available. Measures of effect will be determined by the outcome tool or instrument used and the design of the studies, given the wide range of symptoms and potential breadth of studies. It is anticipated that standardised mean difference (for continuous outcomes) and odds ratio (OR) or relative risk (for binary outcomes) will be the primary measures of effects. The outcome prioritisation plan may be expanded based on the scope and nature of the literature that is identified. For example, we

Table 2 Tentative search strategy for Medline

| Ovid MEDLINE: Epub ahead of print, in-process and other non-indexed citations, Ovid MEDLINE daily and Ovid MEDLINE <1946-Present> | |
|---|--|
| 1 | (exp SARS-CoV-2/exp COVID-19) and sequela*.ti,ab,kf. |
| 2 | "long COVID".ti,ab,kf,hw. |
| 3 | ((COVID-19 or COVID-19 or "corona virus 2019" or "coronavirus 2019" or SARS-CoV-2 or nCoV or "B.1.1.7" or "B.1.351" or "B.1.1.28" or "B.1.617") adj3 (PASC or sequela* or "post acute" or postacute or prolonged or "long haul*" or chronic or lingering or ongoing or persistent or "long term" or "more than 12 weeks" or "more than 24 weeks")).ti,ab,kf,hw. |
| 4 | or/1–3 |
| 5 | Mental Health/ |
| 6 | exp Mental Disorders/ |
| 7 | exp Neurocognitive Disorders/ |
| 8 | exp Cognition/ |
| 9 | exp Quality of life/ |
| 10 | exp Mental Health Services/ |
| 11 | exp Psychotherapy/ |
| 12 | (mental* or psychiatr* or personality disorder* or post-trauma* or posttrauma* or PTSD or complex trauma or developmental trauma or (disorder* adj2 eating) or hallucinat* or (hear* adj3 voice*) or manic or mania or depress* or anxiet* or bipolar or dysthymi* or phobia* or panic* or obsess* or compulsion* or compulsiv* or OCD or mood* or (affective adj3 disorder*) or suicid* or selfharm* or self-harm* or selfinjur* or self-injur* or psychopath* or internaliz* or externaliz* or attention deficit* or ADHD or oppositional* de* or (regulat* adj3 emotional*) or (dysregulat* adj3 emotion*) or aggress*).ti,ab,kf,hw,jn. |
| 13 | ((emotion* or psycholog*) adj3 distress*).ti,ab,kf,hw. |
| 14 | (wellbeing or well-being or wellness).ti,ab,kf,hw. |
| 15 | "quality of life".ti,ab,kf,hw. |
| 16 | (cognition or cognitive* or neuro*).ti,ab,kf,hw. |
| 17 | ((psychosocial or psycholog* or psychiatr*) adj3 (intervention* or program* or servic* or treatment*)).ti,ab,kf,hw. |
| 18 | (psychoeducation or psycho-education).ti,ab,kf,hw. |
| 19 | (cognitiv therap* or behavior?r* therap* or CBT or DBT).ti,ab,kf,hw. |
| 20 | psychotherap*.ti,ab,kf,hw. |
| 21 | (behav* adj3 (intervention* or program* or servic* or treatment*)).ti,ab,kf,hw. |
| 22 | ((lifestyle* or life style*) adj3 (therap* or intervention*)).ti,ab,kf,hw. |
| 23 | or/5–22 |
| 24 | (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. |
| 25 | exp Randomized Controlled Trial/ |
| 26 | exp Randomized Controlled Trials as Topic/ |
| 27 | exp Controlled Clinical Trial/ |
| 28 | exp Controlled Clinical Trials as Topic/ |
| 29 | Random Allocation/ |
| 30 | Double-Blind Method/ |
| 31 | Single-Blind Method/ |
| 32 | Placebos/ |
| 33 | Control Groups/ |
| 34 | (random* or sham or placebo*).ti,ab,kf,hw. |
| 35 | ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,kf,hw. |
| 36 | ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,kf,hw. |
| 37 | (control* adj3 (study or studies or trial* or group*)).ti,ab,kf. |

Continued

Table 2 Continued

Ovid MEDLINE: Epub ahead of print, in-process and other non-indexed citations, Ovid MEDLINE daily and Ovid MEDLINE <1946-Present>

| | |
|----|---|
| 38 | (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,kf,hw. |
| 39 | allocated.ti,ab,hw. |
| 40 | ((open label or open-label) adj5 (study or studies or trial*).ti,ab,kf,hw. |
| 41 | ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*).ti,ab,kf,hw. |
| 42 | (pragmatic study or pragmatic studies).ti,ab,kf,hw. |
| 43 | ((pragmatic or practical) adj3 trial*).ti,ab,kf,hw. |
| 44 | ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*).ti,ab,kf,hw. |
| 45 | (phase adj3 (III or "3") adj3 (study or studies or trial*).ti,kf,hw. |
| 46 | or/24-45 (CADTH Clinical Trials Filter) |
| 47 | (intervention* study or intervention* studies).ti,ab,kf,hw. |
| 48 | ((("Before after" or "pre post") adj3 (study or studies)).ti,ab,kf,hw. |
| 49 | 4 and 23 and (46 or 47 or 48) |
| 50 | limit 49 to yr="2020 -Current" |

may include additional secondary outcomes with neuropsychological relevance, such as pain, headache and fatigue, depending on the nature of the data.

Data synthesis

Data will be summarised in narrative and table format. We will descriptively report on the number, types and characteristics of the interventions identified. We will also provide a narrative summary of their efficacy following the Synthesis Without Meta-Analysis guidelines,²⁹ if a meta-analytical stage is not warranted. If sufficient trials are found that provide treatment efficacy data suitable for a meta-analysis, we will conduct meta-analyses using random effects modelling with RevMan V.5.4.³⁰ We hypothesise that the trials will have different underlying true effects; with that assumption, random-effects models are more appropriate than fixed-effects

models.³¹ For the standardised mean difference, we will use group mean difference and pooled SD. We will also look at ORs and risk ratios as effect sizes for dichotomous outcomes. The heterogeneity between studies will be assessed using a forest plot visually, as well as with the I^2 statistic, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions.³² The meta-regression approach, if feasible, will be used to help understand the sources of heterogeneity. Subgroup analyses will depend on the nature and quantity of data retrieved, due to the variability of symptoms across individuals and the variability of the trials under way. If possible, we will consider subgroup analyses based on gender and other sociodemographic variables (Gender-Based Analysis Plus).³³ The decision to perform subgroup analysis/meta-regression will be first

Table 3 Data extraction plan

| Category | Variables to be extracted |
|-------------------------------|---|
| Basic descriptive information | Country, city, publication reference, trial year(s), funder, report type, peer-review status |
| Research question(s) | Primary and secondary objectives, research questions, aims |
| Participant characteristics | Age, sex, gender, ethnicity |
| Intervention characteristics | Intervention name, intervention description, dose, delivery format, type of administering professional |
| Study design | Controlled trial (control group), longitudinal (number of assessments, timeline of assessments) |
| Methodological components | Inclusion criteria, exclusion criteria, long COVID definition, randomisation, masking, control group description, sample size, timing of assessments |
| Measures | Primary outcomes measures, secondary outcome measures |
| Outcomes | Primary outcomes: mental health (eg, depression, anxiety, other mental health variables), cognition, psychological well-being (eg, general well-being, quality of life) Secondary outcomes: if appropriate based on the resulting literature, physical and neuropsychological outcomes may be reported on Intervention and control group means, SD, SEs, p values, effect sizes, ORs, relative risk |



driven by the research questions (eg, gender effect). The number of studies that contain information about the subgroup in question will determine whether the subgroup analysis is feasible.

Assessment of study quality and bias

We will conduct a number of activities to assess the body of research identified using the Cochrane Risk-of-Bias 2.0 tool for randomised studies.³⁴ For non-randomised studies, we will use the ROBINS-I tool.³⁵ A risk of bias assessment will be conducted with a bias assessment team of two independent study staff, supported by discussions with the study lead to resolve any disagreements. Generalisability indices, including C-statistics, standardised mean difference and Tipton's index,³⁶ will be calculated using the demographic characteristics of the identified samples, such as age and gender; this will serve to determine the degree to which the body of evidence is generalisable to the population. If meta-analyses are conducted, sensitivity analyses will be conducted to ensure that the pooled results are not unduly influenced by one study; this will entail repeated analyses of the primary analysis, with each study deleted from the pool one at a time. The resulting pooled effects of these sensitivity analyses will then be compared with that of the primary analysis. This process may identify studies that have had a high influence on the overall findings. The certainty of the evidence³⁷ and the publication bias³⁴ will also be assessed if the nature of the data permit.

Patient and public involvement

From a patient-oriented research perspective,³⁸ patients with lived experience of long COVID and associated challenges in mental health, cognition or psychological well-being (ie, 'patient partners') will be engaged in the conduct of this review. Patient partners will help refine the search plan and data extraction tool and will help co-interpret the findings to ensure that the information obtained is relevant to their real-world experience.

Strengths and limitations

This study will provide a time-sensitive synthesis of the literature examining the efficacy interventions aiming to promote mental health, cognition or psychological well-being among individuals with long COVID, to support further research, service development and implementation initiatives. The inclusion criteria are intentionally broad due to the dearth of literature available at the time of protocol development. However, the amount of research available for review may change rapidly, as COVID-19 research has emerged at an extremely rapid pace.²² Therefore, it may become necessary to be more restrictive and adjust the draft search terms based on the emerging literature. Any literature released after the date of the updated database search will not be included and could be substantial. The review is further limited by the search in English-language and Chinese-language databases, the inclusion of English, French and Chinese

full-text literature and English-language translations of abstracts only for literature published in another language; these factors will limit the generalisability of the findings.

ETHICS AND DISSEMINATION

This systematic review is not subject to research ethics board approval as there will be no participant contact or direct data collection activities. Knowledge translation will include publication of a systematic review manuscript in an open access journal to reduce barriers and provide ease of access to stakeholders outside of academic structures. The findings will further be presented at national and international conferences with research and clinical audiences. We may present the findings in webinar format for ongoing online, international access by stakeholders interested from both research and clinical perspectives. Other lay knowledge translation opportunities may be identified by the patient partner team.

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Contributors LH conceptualised and designed the review and drafted the manuscript. CFS, WW, DRT, SLR, GS, EB, DX contributed to the design of the review and edited and approved the manuscript. TR contributed to the design of the review, designed the library database search and edited and approved the manuscript. DC contributed to the conceptualisation and design of the review and edited and approved the manuscript.

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Disclaimer The funder had no role in the development of this protocol.

Competing interests DC has received grant monies for research from Servier, Boehringer Ingelheim; travel support and honoraria for talks and consultancy from Servier, Seqirus, Lundbeck. He is a founder of the Optimal Health Program (OHP), and holds 50% of the IP for OHP; and is part owner of Clarity Healthcare. He does not knowingly have stocks or shares in any pharmaceutical company.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this protocol, but will be involved in the conduct of the subsequent research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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