



Topic Brief: Treatment of Post-Acute COVID Sequelae

Date: 9/29/2022

Nomination Number: 1008

Purpose: This document summarizes the information addressing a nomination submitted on June 3, 2022, through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: The nominator of this topic is interested in treatments of post-acute sequelae of COVID for adults, adolescents and children. They represent a national health care delivery organization, and plan to use an AHRQ systematic review to inform national guidance. While this group has an infrastructure for evidence review and guideline development, they do not have the resources to maintain a living review.

[Link to nomination](#)

Recommendation

- Systematic review
- Technical brief
- Evidence map
- Rapid review-living
- Rapid response
- Expanded topic brief

Key Findings

- We found multiple systematic reviews that address the topic, but they did not assess all interventions and age groups.
- We identified a handful of studies. However, there are many more studies in the pipeline on a variety of interventions, including pharmacologic treatments.
- There are ongoing international guideline development efforts that include routine surveillance and updating.
- Considering the pace and volume of literature a living approach to evidence synthesis may be best.

Background

The World Health Organization (WHO) defined the post COVID-19 condition as a condition that occurs in individuals with a history of SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by another diagnosis¹. Symptoms can be new and may fluctuate over time. Greenhalgh et al² uses the terms ‘post-acute COVID-19’ (from 3 to 12 weeks) and ‘chronic COVID-19’ for symptoms extending beyond 12 weeks. In contrast the National Institute for Health and Care

Excellence³ uses the term “ongoing symptomatic COVID19” for symptoms 4-12 weeks from onset; and post-COVID19 syndrome for symptoms 12 weeks and beyond. The term “long COVID” has typically included symptoms from 4 weeks on.

Many terms are used including long COVID, long-haul COVID, post-acute COVID-19, post-acute sequelae of SARS CoV-2 infection (PASC), post-COVID condition, long-term effects of COVID, and chronic COVID⁴.

Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may vary in children and adolescents¹. A recent systematic review concluded that more than half of COVID-19 survivors experienced PASC 6 months after recovery. The most common symptoms related to functional mobility impairments, pulmonary abnormalities, and mental health disorders⁵.

A recent summary of guidelines from the Canadian Agency for Drugs and Technologies in Health (CADTH) found that the most common areas addressed by the literature were diagnosis and treatment, and rehabilitation for PASC. These areas addressed by 11 different guidelines. The area with the least amount of literature was screening for post-COVID-19 condition, included in 4 guidelines. Most guidelines address all age groups, and some include recommendations for specific age groups. Most do not include recommendations addressing coexisting conditions⁶.

There is ongoing international collaboration of guideline developers and evidence synthesis group, including the National Institute for Health and Care Excellence (NICE), WHO, National COVID19 Evidence Task Force, CADTH, Public Health Agency of Canada, and Danish Health Authority to leverage similar overlapping efforts on PASC. Currently they share searches and compare inclusion in guidance. The National COVID19 Evidence Task Force has leveraged recommendations from NICE and WHO for their own guidance.

The US President released a memorandum in April on the long-term effects of COVID19⁷, indicating that this is an important priority of the administration, and proposes organizing a government-wide response, developing a report on long-term effects of COVID, and developing and implementing a National Research Action Plan.

The nominator represents a national healthcare delivery organization that provides healthcare to 12.6 million members including adults, children and adolescents. They plan to use the AHRQ systematic review to inform national guidance. While their institution has infrastructure for evidence review and guideline development, they do not have the resources to maintain a living review. They indicated that up to this point they have been developing evidence maps leveraging reviews and guidance from NICE, Centers for Disease Control and Prevention (CDC), WHO, and Infection Diseases Society of America (IDSA), with a few other studies added.

Scope

Contextual question: How is post-acute COVID sequelae defined?

Question: What is the effectiveness of treatments for post-acute COVID sequelae (PASC) on outcomes such as morbidity, mortality, quality of life, and health care utilization in

- a. Adults
- b. Adolescents
- c. Children

| | |
|---------------------|--|
| Population | Children, adolescents, and adults with a prior COVID-19 diagnosis with lingering symptoms > 4 weeks after resolution of acute disease. Subgroups: age, comorbidities, severity of COVID infection, duration of symptoms |
| Intervention | Treatments to manage PASC symptoms |
| Comparator | Standard care |
| Outcomes | Provider outcomes (e.g., satisfaction) Patient outcomes (e.g., quality of life, mortality, morbidity, health care utilization) Individual and institutional costs (e.g., patient, provider and health system) |

PASC= post-acute sequelae of SARS CoV-2 infection.

Assessment Methods

See Appendix A.

Summary of Literature Findings

We identified fourteen completed and in-progress evidence reviews; of these one is a living rapid review⁸ (with Cochrane), and two have planned updates⁹⁻¹¹ (for CADTH and WHO). These reviews address a diversity of interventions including physical rehabilitation^{8, 12-15}, pulmonary rehabilitation¹⁶, olfactory dysfunction¹⁷, pharmacologic treatments⁹, nonpharmacologic treatments¹⁸, CAM¹⁹, and mental health conditions²⁰. In addition we identified a rapid systematic review on care models for long COVID²¹. We identified a scoping review from CADTH on the classification of long COVID, risk factors related to developing post-COVID-19 condition, diagnostic tests, interventions to prevent or manage symptoms, and evidence related to health systems for people of all ages; the search ended in December 2021¹¹. CADTH also has an in-progress scoping review on treatment and management, to be completed in November 2022²². Three reviews focused only on adults^{12, 13, 19}, eight on children and adults^{9-11, 14, 17, 18, 20, 21}, and in three the age range was not explicitly stated^{8, 15, 16}. Collectively these reviews have varying search dates, interventions, and populations.

Our targeted scan of primary literature identified 21 published studies, two pre-prints and at least 76 new studies in clinicaltrials.gov (Appendix C). Eight are RCTs. It appears that none of the studies include children or adolescents. In addition the NIH has an ongoing RECOVER COVID Initiative to learn about the long-term effects of COVID²³.

We identified two living guidelines from NICE³ and National COVID19 Evidence Task Force (Australia)²⁴. Both entities use systematic methods for identifying the supporting evidence and weekly surveillance. The guidelines however are specific to the healthcare delivery settings and not applicable to the US healthcare system. The evidence underlying the guidance is available through MAGICapp though both do not publish a separate systematic review.

CADTH plans to commission rapid reviews based on the results of their in-progress scoping review²². Preliminary findings from their scoping review may be available in November. The scoping review will have quarterly surveillance.

| Key question | Systematic reviews (August 2021-August 2022) | Study publications (August 2020-August 2022) |
|--------------------------|--|---|
| KQ 1: treatment for PASC | Total-14 Interventions to prevent or manage symptoms-2 <ul style="list-style-type: none"> CADTH scoping review with planned update^{10, 11, 22} | Total-23 publications Pharmacologic treatment-4 ²⁵⁻²⁸ <ul style="list-style-type: none"> Non-RCT-4 Pre-print (cluster randomized)-1²⁹ Rehabilitation-7 |

| | |
|---|--|
| <ul style="list-style-type: none"> Pharmacologic treatment-1 <ul style="list-style-type: none"> • PROSPERO-for WHO with planned update next year⁹ Non-pharmacologic treatment-1 <ul style="list-style-type: none"> • PROSPERO-1¹⁸ Rehabilitation-5 <ul style="list-style-type: none"> • Pubmed-2^{12, 13} • Cochrane living review⁸ • PROSPERO-2^{14, 15} Pulmonary rehabilitation-1 <ul style="list-style-type: none"> • PROSPERO-1¹⁶ Mental health-1 <ul style="list-style-type: none"> • WHO database-1²⁰ (scoping review) Olfactory-1 <ul style="list-style-type: none"> • Cochrane-1¹⁷ CAM-1 <ul style="list-style-type: none"> • PROSPERO-1¹⁹ Care models-1²¹ | <ul style="list-style-type: none"> • RCT-3³⁰⁻³² • Non-RCT-4³³⁻³⁶ • Pre-print (RCT)-1³⁷ Pulmonary rehab-1 <ul style="list-style-type: none"> • Non-RCT-1³⁵ Mental health-0 Olfactory-3 <ul style="list-style-type: none"> • RCT-1³⁸ • Non-RCT-2^{39, 40} CAM-6 <ul style="list-style-type: none"> • RCT-3^{10, 41-43} • Non-RCT-3⁴⁴⁻⁴⁶ |
|---|--|

PASC= post-acute sequelae of SARS CoV-2 infection; KQ=key question; RCT=randomized controlled trial.

Summary of Selection Criteria Assessment

This is an important and increasingly prevalent condition. We found many systematic reviews and are aware of living guidelines in the UK and Australia. Discussion with National COVID19 Evidence Task Force affirmed the need for a regularly updated publicly available free-standing comprehensive and rigorous systematic review. CADTH has expressed interest in collaborating and coordinating with AHRQ to commission complementary living rapid reviews related to post-COVID treatments. This topic is of high interest to many entities including the Biden administration, international guideline developers, clinical groups, and PCORI.

Considering the pace and volume of research; the evolving understanding of the condition, case definitions, and treatments in the pipeline; and the need for coordination with a partner for guideline development, we recommend a living rapid review. We recommend that AHRQ coordinate with CADTH and other groups on scope of the review to avoid duplication. Depending on the breadth of the review scope and size of the literature base, more than one rapid review may be desired. In addition, we recommend that if funded the review should include ongoing engagement with the aforementioned international collaboration of guideline developers; continued coordination and communication with other evidence synthesis groups; flexibility to update review questions and scope to maintain relevance and feasibility; and plans to increase efforts as the literature base increases.

Related Resources

Other reviews related to PASC that may be of interest to the nominator:

- Subtypes of Post-COVID-19 Condition, published by CADTH⁴⁷
- Evidence Compendium: Long-term Effects of SARS-CoV-2 Infection (COVID-19) on Functional Health Status and Health-related Quality of Life in Community-dwelling Adults. Published by the VA Evidence Synthesis Program⁴⁸
- Evidence brief: employment, education, and continuing care outcomes among individuals following COVID-19. Authors are from the Minneapolis VA Medical Center.⁴⁹

References

1. Soriano JB, Murthy S, Marshall JC, et al. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*. 2022 Apr;22(4):e102-e7. doi: 10.1016/S1473-3099(21)00703-9. PMID: 34951953.
2. Greenhalgh T, Knight M, A'Court C, et al. Management of post-acute covid-19 in primary care. *BMJ*. 2020 Aug 11;370:m3026. doi: 10.1136/bmj.m3026. PMID: 32784198.
3. Shah W, Hillman T, Playford ED, et al. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. *BMJ*. 2021 Jan 22;372:n136. doi: 10.1136/bmj.n136. PMID: 33483331.
4. Long COVID or Post-COVID Conditions. Atlanta, GA: Centers for Disease Control and Prevention; 2022. <https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html#:~:text=behind%20Long%20COVID-20Symptoms,away%20or%20come%20back%20again.2022>.
5. Groff D, Sun A, Ssentongo AE, et al. Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection: A Systematic Review. *JAMA Netw Open*. 2021 Oct 1;4(10):e2128568. doi: 10.1001/jamanetworkopen.2021.28568. PMID: 34643720.
6. Haas R. CADTH Health Technology Review: Post-COVID-19 Condition, Summary of Guidelines. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health; 2022. <https://www.cadth.ca/sites/default/files/ou-tr/HC0037-Post-COVID-19-Conditions-Guideline.pdf>.
7. Memorandum on Addressing the Long-Term Effects of COVID-19. Washington, DC: The White House; 2022. <https://www.whitehouse.gov/briefing-room/presidential-actions/2022/04/05/memorandum-on-addressing-the-long-term-effects-of-covid-19/>.
8. de Sire A, Andrenelli E, Negrini F, et al. Rehabilitation and COVID-19: update of the rapid living systematic review by Cochrane Rehabilitation Field as of February 28th, 2022. *Eur J Phys Rehabil Med*. 2022 Jun;58(3):498-501. doi: 10.23736/S1973-9087.22.07593-1. PMID: 35612401.
9. Rahman KM KK, Sadlier C, Moriarty F, Movsisyan A, Whelan S, Taneri PE, Blair M, Devane D. Effect of pharmacological interventions for the treatment of people with post-COVID-19 condition. PROSPERO; 2022. https://www.crd.york.ac.uk/prospéro/display_record.php?ID=CRD420223308732022.
10. Post-COVID-19 Condition: A Condition-Level Review. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health. <https://www.cadth.ca/post-covid-19-condition-condition-level-review2022>.
11. Chao YS VT, McGill SC, Gates M. CADTH Health Technology Review: Clinical Classification and Interventions for Post-COVID-19 Condition: A Scoping Review. *Canadian Journal of Health Technologies*. 2022 May 2022;2(5).
12. Bailly M, Pelissier L, Coudeyre E, et al. Systematic Review of COVID-19-Related Physical Activity-Based Rehabilitations: Benefits to Be Confirmed by More Robust Methodological Approaches. *Int J Environ Res Public Health*. 2022 Jul 25;19(15). doi: 10.3390/ijerph19159025. PMID: 35897400.
13. Fugazzaro S, Contri A, Esseroukh O, et al. Rehabilitation Interventions for Post-Acute COVID-19 Syndrome: A Systematic Review. *Int J Environ Res Public Health*. 2022 Apr 24;19(9). doi: 10.3390/ijerph19095185. PMID: 35564579.
14. Kannan A RK, Perez BD. A systematic review on effectiveness of musculoskeletal physical therapy rehabilitation on quality of life in post Covid population. PROSPERO; 2022. https://www.crd.york.ac.uk/prospéro/display_record.php?ID=CRD420223127872022.

15. Al-Mhanna S GW. Effectiveness of physical activity and rehabilitation on physical function and quality of life of COVID -19 survivor : a systematic review. PROSPERO; 2022. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD420212830872022.
16. OLIVEIRA M B-SA, Holland A, Jones A, Hoffman M, Lahham A. Effect of pulmonary rehabilitation on dyspnea, fatigue, peripheral muscle strength and exercise capacity in Post-Covid patients: a systematic review and meta-analysis. PROSPERO; 2022. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD420223107882022.
17. O'Byrne L, Webster KE, MacKeith S, et al. Interventions for the treatment of persistent post-COVID-19 olfactory dysfunction. Cochrane Database Syst Rev. 2021 Jul 22;7:CD013876. doi: 10.1002/14651858.CD013876.pub2. PMID: 34291813.
18. Igwesi-Chidobe C OE, Emmanuel G. Characterisation of long COVID and the effectiveness of non-pharmacological treatments: a systematic review. PROSPERO; 2022. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD420223212812022.
19. Cafe AC LJ, Romano CC, Quinte GC, Novaes RL. Association between food consumption, emotional eating and spirituality with a post Covid-19 conditions: systematic review. PROSPERO; 2022. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD420223294332022.
20. Chennapragada L, Sullivan SR, Hamerling-Potts KK, et al. International PRISMA scoping review to understand mental health interventions for depression in COVID-19 patients. Psychiatry Res. 2022 Jul 25;316:114748. doi: 10.1016/j.psychres.2022.114748. PMID: 35944370.
21. Decary S DM, Stefan T, Langlois L, Skidmore B, Bhéreur A, and, A. L. Care Models for Long COVID: A Rapid Systematic Review. Quebec, Canada: SPOR Evidence Alliance, COVID-END Network; 2021. https://sporevidencealliance.ca/wp-content/uploads/2021/06/Care-Models-for-Long-COVID_Full-Report_2021.06.18.pdf.
22. Post COVID-19 Condition Treatment and Management Scoping Review. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health; 2022. <https://www.cadth.ca/post-covid-19-condition-treatment-and-management-scoping-review2022>.
23. RECOVER: Researching COVID to Enhance Recovery. Bethesda, MD: National Institutes of Health; 2022. <https://recovercovid.org/>. Accessed on 16 September 2022 2022.
24. Caring for people with COVID-19: Supporting Australia's healthcare professionals with continually updated, evidence-based clinical guidelines. Melbourne, Australia: National COVID=19 Clinical Evidence Task Force. <https://covid19evidence.net.au/#living-guidelines>. Accessed on 19 August 2022 2022.
25. Cash A, Kaufman DL. Oxaloacetate Treatment For Mental And Physical Fatigue In Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Long-COVID fatigue patients: a non-randomized controlled clinical trial. J Transl Med. 2022 Jun 28;20(1):295. doi: 10.1186/s12967-022-03488-3. PMID: 35764955.
26. Catalán IP, Martí CR, Sota DP, et al. Corticosteroids for COVID-19 symptoms and quality of life at 1 year from admission. J Med Virol. 2022 Jan;94(1):205-10. doi: 10.1002/jmv.27296. PMID: 34436783.
27. Charfeddine S, Ibnhadjamor H, Jdidi J, et al. Sulodexide Significantly Improves Endothelial Dysfunction and Alleviates Chest Pain and Palpitations in Patients With Long-COVID-19: Insights From TUN-EndCOV Study. Front Cardiovasc Med. 2022;9:866113. doi: 10.3389/fcvm.2022.866113. PMID: 35647070.
28. Samartsev IN, Zhivolupov SA, Butakova JS, et al. [The open observational study of aceclofenac and vinpocetine effectiveness and tolerability in treatment of patients with chronic cerebrovascular disease after COVID-19 (AQUA study)]. Zh Nevrol Psikhiatr Im S S Korsakova. 2021;121(11):s1-s8. doi: 10.17116/jnevro2021121111s1. PMID: 34968019.

29. Forshaw D, Wall EC, Prescott G, et al. STIMULATE-ICP: A pragmatic, multi-centre, cluster randomised trial of an integrated care pathway with a nested, Phase III, open label, adaptive platform randomised drug trial in individuals with Long COVID: a structured protocol. medRxiv. 2022:2022.07.21.22277893. doi: 10.1101/2022.07.21.22277893.
30. Besnier F, Bérubé B, Malo J, et al. Cardiopulmonary Rehabilitation in Long-COVID-19 Patients with Persistent Breathlessness and Fatigue: The COVID-Rehab Study. *Int J Environ Res Public Health*. 2022 Mar 31;19(7). doi: 10.3390/ijerph19074133. PMID: 35409815.
31. Poncin W, Schalkwijk A, Vander Straeten C, et al. Impact of surgical mask on performance and cardiorespiratory responses to submaximal exercise in COVID-19 patients near hospital discharge: A randomized crossover trial. *Clin Rehabil*. 2022 Aug;36(8):1032-41. doi: 10.1177/02692155221097214. PMID: 35473371.
32. Morrow A, Gray SR, Bayes HK, et al. Prevention and early treatment of the long-term physical effects of COVID-19 in adults: design of a randomised controlled trial of resistance exercise-CISCO-21. *Trials*. 2022 Aug 15;23(1):660. doi: 10.1186/s13063-022-06632-y. PMID: 35971155.
33. Curci C, Pisano F, Bonacci E, et al. Early rehabilitation in post-acute COVID-19 patients: data from an Italian COVID-19 Rehabilitation Unit and proposal of a treatment protocol. *Eur J Phys Rehabil Med*. 2020 Oct;56(5):633-41. doi: 10.23736/s1973-9087.20.06339-x. PMID: 32667150.
34. Estebanez-Pérez MJ, Pastora-Bernal JM, Martín-Valero R. The Effectiveness of a Four-Week Digital Physiotherapy Intervention to Improve Functional Capacity and Adherence to Intervention in Patients with Long COVID-19. *Int J Environ Res Public Health*. 2022 Aug 3;19(15). doi: 10.3390/ijerph19159566. PMID: 35954922.
35. Nopp S, Moik F, Klok FA, et al. Outpatient Pulmonary Rehabilitation in Patients with Long COVID Improves Exercise Capacity, Functional Status, Dyspnea, Fatigue, and Quality of Life. *Respiration*. 2022;101(6):593-601. doi: 10.1159/000522118. PMID: 35203084.
36. Bures M, Neumannova K, Blazek P, et al. A Sensor Network Utilizing Consumer Wearables for Telerehabilitation of Post-acute COVID-19 Patients. *IEEE Internet of Things Journal*. 2022:1-. doi: 10.1109/JIOT.2022.3188914.
37. Simon Hatcher JW, Nicole E Edgar et al. . Enhancing COVID Rehabilitation with Technology (ECORT): Protocol for an open-label, single site randomized controlled trial evaluating the effectiveness of electronic case management for individuals with persistent COVID-19 symptoms. *Research Square* 2022 26 July 2022;PREPRINT (Version 1) doi: <https://doi.org/10.21203/rs.3.rs-1723719/v1>.
38. Pires IAT, Steffens ST, Mocelin AG, et al. Intensive Olfactory Training in Post-COVID-19 Patients: A Multicenter Randomized Clinical Trial. *Am J Rhinol Allergy*. 2022 Jul 21:19458924221113124. doi: 10.1177/19458924221113124. PMID: 35866202.
39. Steffens Y, Le Bon SD, Lechien J, et al. Effectiveness and safety of PRP on persistent olfactory dysfunction related to COVID-19. *Eur Arch Otorhinolaryngol*. 2022 Jul 29. doi: 10.1007/s00405-022-07560-y. PMID: 35904632.
40. Yaylaci A, Azak E, Onal A, et al. Effects of classical olfactory training in patients with COVID-19-related persistent loss of smell. *Eur Arch Otorhinolaryngol*. 2022 Jul 29. doi: 10.1007/s00405-022-07570-w. PMID: 35904631.
41. Hawkins J, Hires C, Keenan L, et al. Aromatherapy blend of thyme, orange, clove bud, and frankincense boosts energy levels in post-COVID-19 female patients: A randomized, double-blinded, placebo controlled clinical trial. *Complement Ther Med*. 2022 Aug;67:102823. doi: 10.1016/j.ctim.2022.102823. PMID: 35341944.
42. Kharaeva Z, Shokarova A, Shomakhova Z, et al. Fermented *Carica papaya* and *Morinda citrifolia* as Perspective Food Supplements for the Treatment of Post-COVID Symptoms:

- Randomized Placebo-Controlled Clinical Laboratory Study. *Nutrients*. 2022 May 25;14(11). doi: 10.3390/nu14112203. PMID: 35684003.
43. Raghavan K, Dedeepiya VD, Suryaprakash V, et al. Beneficial effects of novel *aureobasidium pullulans* strains produced beta-1,3-1,6 glucans on interleukin-6 and D-dimer levels in COVID-19 patients; results of a randomized multiple-arm pilot clinical study. *Biomed Pharmacother*. 2022 Jan;145:112243. doi: 10.1016/j.biopha.2021.112243. PMID: 34840031.
44. Orendacova M, Kvasnak E, Vranova J. Effect of neurofeedback therapy on neurological post-COVID-19 complications (A pilot study). *PLoS One*. 2022;17(7):e0271350. doi: 10.1371/journal.pone.0271350. PMID: 35895740.
45. Rossato MS, Brilli E, Ferri N, et al. Observational study on the benefit of a nutritional supplement, supporting immune function and energy metabolism, on chronic fatigue associated with the SARS-CoV-2 post-infection progress. *Clin Nutr ESPEN*. 2021 Dec;46:510-8. doi: 10.1016/j.clnesp.2021.08.031. PMID: 34857243.
46. Tirelli U, Franzini M, Valdenassi L, et al. Fatigue in post-acute sequelae of SARS-CoV2 (PASC) treated with oxygen-ozone autohemotherapy - preliminary results on 100 patients. *Eur Rev Med Pharmacol Sci*. 2021 Sep;25(18):5871-5. doi: 10.26355/eurrev_202109_26809. PMID: 34604980.
47. Subtypes of Post-COVID-19 Condition. Ottawa, Canada: Canada's Drug and Health Technology Agency; 2022. <https://www.cadth.ca/subtypes-post-covid-19-condition>. Accessed on 28 September 2022 2022.
48. Gustavson AM GN, Sowerby K, Ensrud KE, Hill JE, Kaka A, Wilt TJ. Evidence Compendium: Long-term Effects of SARS-CoV-2 Infection (COVID-19) on Functional Health Status and Health-related Quality of Life in Community-dwelling Adults. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs; 2022. <https://www.hsrd.research.va.gov/publications/esp/long-covid-compendium.cfm>.
49. Greer N DS, Sowerby K, Wilt T. Evidence brief: employment, education, and continuing care outcomes among individuals following COVID-19. PROSPERO; 2022. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=337281.
50. Cutler DM, Summers LH. The COVID-19 Pandemic and the \$16 Trillion Virus. *JAMA*. 2020 Oct 20;324(15):1495-6. doi: 10.1001/jama.2020.19759. PMID: 33044484.
-

Author

Christine Chang

Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgements

Mark Helfand

This report was developed by staff of Agency for Healthcare Research and Quality (AHRQ), Rockville, MD. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be

construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EPC@ahrq.hhs.gov.

Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We conducted a search for existing systematic reviews. We searched for high-quality, completed or in-process evidence reviews published in the last year August 2021 to August 2022 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
 - AHRQ Evidence Reports <https://www.ahrq.gov/research/findings/evidence-based-reports/index.html>
 - EHC Program <https://effectivehealthcare.ahrq.gov/>
- US Department of Veterans Affairs Products publications
 - Evidence Synthesis Program <https://www.hsrd.research.va.gov/publications/esp/>
 - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program <https://www.healthquality.va.gov/>
- Cochrane Systematic Reviews <https://www.cochranelibrary.com/>
- PROSPERO Database (international prospective register of systematic reviews and protocols) <http://www.crd.york.ac.uk/prospero/>
- PubMed <https://www.ncbi.nlm.nih.gov/pubmed/>
- Canadian Agency for Drugs and Technologies in Health <https://www.cadth.ca/>
- [WHO COVID-19 Database](#)

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (such as practice recommendation, clinical guidelines, clinical pathways).

Feasibility of New Evidence Review

We conducted a limited search of primary literature from: Medline published within the last 2 years from August 2020 through August 2022; clinicaltrials.gov; and WHO database. We reviewed the entire search yield for Medline and Clinicaltrials.gov for relevance. We reviewed the first 300 entries from the WHO database for relevance. The WHO database includes entries from MedRxiv so an additional search for pre-prints was not felt to be necessary.

Medline: Searched 8/18/2022

(((((("Long COVID") OR ("long-haul COVID")) OR ("post-acute COVID")) OR ("post-acute sequelae of SARS CoV-2 infection")) OR (PASC)) OR ("chronic COVID"))

Clinical Trials, searched 8/18/2022

<https://clinicaltrials.gov/ct2/results?cond=Long+COVID&term=&cntry=&state=&city=&dist=>

WHO Database, searched 8/19/2022

type_of_study:("observational_studies" OR "rct" OR "qualitative_research" OR "evaluation_studies" OR "clinical_trials") AND covidwho_topics:("long_covid") AND la:("en")

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change, if a partner organization would use this evidence review to influence practice, and if the topic supports a priority area of AHRQ or the Department of Health and Human Services.

Appendix B. Selection Criteria Assessment

| Selection Criteria | Assessment |
|--|---|
| 1. Appropriateness | |
| 1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.? | Yes. Treatment for long COVID is available in the US. |
| 1b. Is the nomination a request for an evidence report? | The nominator is interested in guidance to assist in healthcare decision-making. Such guidance would ideally be supported by an evidence review. |
| 1c. Is the focus on effectiveness or comparative effectiveness? | Yes. The nominator is interested in effectiveness and harms of treatment. |
| 1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic? | Yes. |
| 2. Importance | |
| 2a. Represents a significant disease burden; large proportion of the population | It is estimated that 7.7–23 million people have PASC (https://www.gao.gov/products/gao-22-105666). The most common symptoms related to functional mobility impairments, pulmonary abnormalities, and mental health disorders. |
| 2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population | Yes, this is of high interest |
| 2c. Incorporates issues around both clinical benefits and potential clinical harms | Yes. The nominator is interested in both benefits and harms, especially for important subgroups |
| 2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers | It has been estimated that the COVID-19 pandemic might result in \$2.6 trillion of cost for long COVID ⁵⁰ . |
| 3. Desirability of a New Evidence Review/Absence of Duplication | |
| 3. A recent high-quality systematic review or other evidence review is not available on this topic | We identified 13 completed and in-progress evidence reviews. Of the 13, one may be updated in the next year and another is an update of a completed scoping review. We also identified two living guidelines, one from NICE and the other from Australia. Both have systematic methods for identifying evidence underpinning the guidelines. |
| 4. Impact of a New Evidence Review | |
| 4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)? | Yes, the standard of care is unclear because of the limited evidence. There is available guidance from multiple bodies internationally, including the UK, Australia, and WHO. There is also guidance from clinical specialties such as AAPMR (https://onlinelibrary.wiley.com/doi/full/10.1002/pmjr.12684) and AAP (https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/post-covid-19-conditions-in-children-and-adolescents/). |
| 4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)? | There is practice variation because of the lack of evidence. |
| 5. Primary Research | |

| | |
|---|--|
| <p>5. Effectively utilizes existing research and knowledge by considering:</p> <ul style="list-style-type: none"> - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies) | <p>We identified 23 studies in the targeted search, and at least 76 ongoing studies. Though the studies are few, we anticipate that there will be a dramatic increase in newly available evidence.</p> |
| <p>6. Value</p> | |
| <p>6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change</p> | <p>Yes. There is high-interest in this topic internationally. It is a priority for the Biden administration and many clinical groups. In addition PCORI has expressed interest in this topic.</p> |
| <p>6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)</p> | <p>The nominator represents a healthcare delivery organization of over 12 million patients. They plan to develop guidance with the AHRQ systematic review.</p> <p>In addition, this review could be helpful to inform guidance internationally and foster collaboration with evidence synthesis groups and guideline developers internationally.</p> |

Appendix C: Relevant in-progress Studies, Clinicaltrials.gov (searched 8/18/2022)

Pharmacologic treatment

1. [Impact of Monoclonal Antibody Treatment on Post-Acute COVID-19 Syndrome](#)
2. [Effects of Sodium Pyruvate Nasal Spray in COVID-19 Long Haulers. Has results](#)
3. [Clinical Trial of Niagen to Examine Recovery in People With Persistent Cognitive and Physical Symptoms After COVID-19 Illness \(Long-COVID\)](#)
4. [Pilot Study Into LDN and NAD+ for Treatment of Patients With Post-COVID-19 Syndrome](#)
5. [Efficacy of Montelukast in Mild-moderate Respiratory Symptoms in Patients With Long-COVID-19:](#)
6. [Clinical Trial of Efficacy and Safety of Prospekta in the Treatment of Post-COVID-19 Asthenia.](#)
7. [Statin Treatment for COVID-19 to Optimise Neurological recovery](#)
8. [Ivabradine for Long-Term Effects of COVID-19 With POTS Cohort](#)
9. [Temelimab as a Disease Modifying Therapy in Patients With Neuropsychiatric Symptoms in Post-COVID 19 or PASC Syndrome](#)
10. [Zofin to Treat COVID-19 Long Haulers](#)
11. [Vortioxetine for Post-COVID-19 Condition](#)
12. [Low-dose Naltrexone for Post-COVID Fatigue Syndrome](#)
13. [SOLIDARITY Finland Plus Long-COVID](#)
14. [SOLIDARITY Finland Long-COVID \(Remdesivir Long-term Follow-up Study of COVID Patients\)](#)

Investigational medications

1. [Phase 2 Study of RSLV-132 in Subjects With Long COVID](#)
2. [A Phase 2 Study to Evaluate the Efficacy and Safety of TNX-102 SL in Patients With Multi-Site Pain Associated With Post-Acute Sequelae of SARS-CoV-2 Infection](#)
3. [BIO 300 Oral Suspension in Previously Hospitalized Long COVID Patients](#)
4. [Safety, Tolerability and Efficacy of S-1226 in Post-COVID-19 Subjects With Persistent Respiratory Symptoms.](#)
5. [Effects of PEA-LUT on Frontal Lobe Functions and GABAergic Transmission in Long-Covid Patients](#)
6. [A Study to Evaluate Ampion in Patients With Prolonged Respiratory Symptoms Due to COVID-19 \(Long COVID\)](#)
7. [Efficacy, Safety, Tolerability of AXA1125 in Fatigue After COVID-19 Infection](#)
8. [LYT-100 in Post-acute COVID-19 Respiratory Disease](#)

CAM

1. [Feasibility of Cannabidiol for the Treatment of Long COVID](#)
2. [Double-Blind Randomized Placebo-Controlled Trial of a Proprietary Full Hemp Flower Formulation for Long COVID](#)
3. [Homeopathic Treatment of Post-acute COVID-19 Syndrome](#)
4. [SingStrong: Strong Lungs Through Song - Long COVID-19 Study](#)
5. [The Effect of Micellized Food Supplements on Health-related Quality of Life in Patients With Post-acute COVID-19 Syndrome.](#)
6. [WHO COVID-19 - Evaluation of the Efficacy of Probiotics to Reduce the Occurrence of Long COVID](#)
7. [Safety and Efficacy of Hyperbaric Oxygen Therapy for Long COVID Syndrome](#)
8. [TaiChi-DTx for Treating Long Covid Symptoms](#)
9. [Portable Oxygen Concentrator \(POC\) Versus Standard of Care in Long-COVID: Randomized Crossover Exploratory Pilot Study.](#)

10. [Randomised Study to Investigate the Effectiveness of Acupuncture for the Relief of Long COVID-19 Related Fatigue](#)
11. [HEART Rate Variability Biofeedback in Long COVID-19 \(HEARTLOC\)](#)
12. [Yogic Breathing and Guided Meditation for Long Covid Symptoms](#)
13. [Study to Evaluate Benefits & Safety of Endourage Formula C™ Oral Drops in People With Post-Acute COVID-19 Syndrome.](#)
14. [Mind Body Intervention for COVID-19 Long Haul Syndrome](#)
15. [Coenzyme Q10 as Treatment for Long Term COVID-19](#)
16. [Feasibility Pilot Clinical Trial of Omega-3 Supplement vs. Placebo for Post Covid-19 Recovery Among Health Care Workers](#)
17. [Efficacy of Adaptogens in Patients With Long COVID-19](#)

Physical rehabilitation, exercise

1. [Long-term COVID and Rehabilitation](#)
2. [Exercise and Post-COVID/ Long-COVID: Effects of Different Training Modalities on Various Parameters in People Affected by the Sequelae of COVID-19](#)
3. [Home-based Exercise Program in Patients With the Post-COVID-19 Condition](#)
4. [A Pilot Study of a PhysiOthErapy-based Tailored Intervention for Long Covid](#)
5. [Long Haul COVID Rehabilitation & Recovery Research Program](#)
6. [Symptom-based Rehabilitation Compared to Usual Care in Post-COVID - a Randomized Controlled Trial](#)
7. [Osteopathy and Physiotherapy Compared to Physiotherapy Alone on Fatigue and Functional Status in Long COVID](#)
8. [Virtual Physical Rehabilitation Following COVID-19 Hospitalization](#)
9. [Physical Training in Patients With POTS After Covid-19](#)
10. [Telerehabilitation Program in Persistent COVID-19](#)
11. [Effectiveness of a Physical Therapy Telerehabilitation Program in Long Post COVID-19 Symptoms in Primary Health Care.](#)
12. [Rehabilitation for Patients With Persistent Symptoms Post COVID-19](#)

Pulmonary rehabilitation

1. [Pulmonary Rehabilitation for Long COVID \(Post COVID-19 Condition\)](#)
2. [Cardiopulmonary Rehabilitation in Long COVID-19 Patients With Persistent Breathlessness and Fatigue](#)
3. [Pulmonary Rehabilitation Post-COVID-19](#)
4. [Inspiratory Muscle Training in ME/CFS and COVID-19 Survivors](#)
5. [Effects of Inspiratory Muscle Training After Covid-19 \(ReCOV\)](#)
6. [Cardiopulmonary Rehabilitation in COVID-19 Longhaulers](#)

Technology

1. [The Impact of a Web-Based Platform for Quality of Life and Muscle Health in Patients With Long COVID: A Pilot Study](#)
2. [Digital Health Intervention Based on Artificial Intelligence to Support the Personalized Recovery of Long COVID Patients Affected by Fatigue \(AIDA\)](#)
3. [Does a Technology Enabled Multi-disciplinary Team-based Care Model for the Management of Long COVID and Other Fatiguing Illnesses Improve Clinical Care of Patients and Represent a Sustainable Approach Within a Federally Qualified Health Center?](#)
4. [Internet-based Multidisciplinary Rehabilitation for Longterm COVID-19 Syndrome](#)
5. [Enhancing COVID Rehabilitation With Technology](#)
6. [Electrical Stimulation for Post Acute COVID-19 Syndrome](#)

7. [BREATHE: Virtual Self-management for Long COVID-19](#)
8. [Covid-19 Virtual Recovery Study](#)

Mental health

1. [Developing an Integrative, Recovery-Based, Post-Acute COVID-19 Syndrome \(PACS\) Psychotherapeutic Intervention](#)
2. [Computer Cognitive Training for Post-acute COVID-19 Syndrome](#)
3. [Long-Covid: Treatment of Cognitive Difficulties](#)
4. [Treatment of COVID-19 Post-acute Cognitive Impairment Sequelae With tDCS](#)

Nerve stimulation

1. [Trial of Auricular Vagus Nerve Stimulation in Painful Covid Long](#)
2. [Effects of Cranial Electrotherapy Stimulation on Anxiety of Patients After COVID-19](#)
3. [Transcranial Direct Stimulation for Persistent Fatigue Treatment Post-COVID-19](#)

Self-management

1. [Self-Management Interventions for Long-COVID](#)
2. [Self-management of Post COVID-19 Syndrome Using Wearable Biometric Technology](#)

Other non-pharmacologic treatment

1. [Immunotherapy for Neurological Post-Acute Sequelae of SARS-CoV-2](#)
2. [Plasma Exchange Therapy for Post- COVID-19 Condition: A Pilot, Randomized Double-Blind Study](#)

Appendix D: Nomination

Treatments for Post-Acute COVID Sequelae

NOMINATED TOPIC | June 3, 2022

1. What is the decision or change (e.g. clinical topic, practice guideline, system design, delivery of care) you are facing or struggling with where a summary of the evidence would be helpful?

Question: What is the effectiveness of treatments for post-acute COVID sequelae (PASC) in the adult and pediatric populations on outcomes such as morbidity, mortality, quality of life, and health care utilization?

Population: Children, adolescents and adults with a prior COVID-19 diagnosis presenting with lingering symptoms > 4 weeks after resolution of acute disease.

Intervention and Comparator: therapeutic treatment that manages PASC symptoms and comorbidities with continued follow-up vs. standard care.

Outcomes:

Provider outcomes (e.g., satisfaction)

Patient outcomes (e.g., quality of life, mortality, morbidity, health care utilization)

individual and institutional costs (e.g., patient, provider and health system)

2. Why are you struggling with this issue?

As the COVID-19 pandemic continues globally, there is increasing need to understand the disease spectrum and strategize for long-term patient management. While many patients diagnosed with COVID-19 see their symptoms resolve after the acute phase, emerging data describes a subgroup of patients with a prolonged course of symptoms lasting several weeks to months. As we attempt to better understand PASC symptoms, prognosis, risk factors, and treatment, variation exists throughout the organization in the provision of health care for adult and pediatric cases. As a living PASC systematic evidence review does not currently exist, a rigorous evidence product developed by the EPC will assist us in identifying effective treatments that can be provided within our health care delivery system and ultimately meet the health needs of our members with PASC.

3. What do you want to see changed? How will you know that your issue is improving or has been addressed?

As a national organization that provides healthcare to 12.6 million members including adults, children and adolescents, Kaiser Permanente strives to develop and refine evidence-based practices to ensure the delivery of efficient and effective health care to all its members. In this case, findings from a rigorous EPC systematic review on this topic can be used to better

understand PASC symptoms, risk factors and prognosis and identify effective treatments to help standardize the provision of care within the organization for these patients.

4. When do you need the evidence report?

Fri, 06/30/2023

5. What will you do with the evidence report?

Findings from this evidence review will be used to inform health care decisions and to develop national guidance for adults and pediatric patients. National COVID-19 and preliminary PASC guidance products are already circulated and shared throughout the organization with clinicians, physician assistants, nurse practitioners, and other health care professionals.

Optional Information About You

What is your role or perspective? Physician

If you are you making a suggestion on behalf of an organization, please state the name of the organization Kaiser Permanente

May we contact you if we have questions about your nomination? Yes