PAHO

Pan American Health Organization

World Health Organization
REGIONAL OFFICE FOR THE Americas

LIVING SYSTEMATIC REVIEW OF THERAPEUTIC OPTIONS FOR POST-ACUTE OR POST-COVID19 CONDITION

April 1 2023

Living Systematic Review of Therapeutic Options for Post Acute or Post COVID-19 Condition

Washington, D.C.

1 April 2023

Living Systematic Review of Therapeutic Options for Post Acute or Post COVID-19 Condition, 1 April 2023

PAHO/IMS/EIH/COVID-19/23-0014

This document includes the results of a rapid systematic review of current available literature. The information included in this review reflects the evidence as of the date posted in the document. In recognition of the fact that there are numerous ongoing clinical studies, PAHO will periodically update this review and corresponding recommendations as new evidence becomes available.

Contents

Acknowledgments

This document was developed by Ariel Izcovich, Martin Ragusa, Fernando Tortosa, Sasha Peiris, and Ludovic Reveiz from the knowledge Translation Program, Department of Evidence and Intelligence for Action in Health and the Incident Management System for the response to COVID-19, Pan American Health Organization (PAHO). It was strengthened with the valuable contributions of: Pedro Ordunez, Antony Duttine and Carmen Martinez from the Noncommunicable Diseases and Mental Health department, PAHO, and Sylvain Aldighieri, Deputy Director of the Health Emergencies and Incident Management System for the response to COVID-19.

Funding

This work was partially funded by the Government of the United States of America.

Executive summary

Background

Post COVID-19 condition (PCC), also known as long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC), is the continuation or development of new symptoms in the period after acute infection with SARS-CoV-2. The World Health Organization (WHO) definition of PCC states that these symptoms should be present after three months of the initial SARS-CoV-2 infection and last for at least two months with no other explanation. While PASC definitions states that persistent or new symptoms need to be present 30 days after a documented SARS-COV-2 infection or the onset of COVID-19 symptoms, post-COVID-19 condition or post-acute sequelae of SARS-CoV-2 infection (P-ACC) can affect anyone exposed to SARS-CoV-2, regardless of age or severity of acute infection. Many of the reported symptoms are debilitating and have a strong negative impact on mental health and the quality of life. While most patients recover, some may experience multiple outcomes, with multiple organ systems affected simultaneously, including cardiovascular, mental, metabolic, renal, and others.

This review compiles the following evidence on potential therapeutic options for P-ACC. It includes all the identified clinical forms, symptoms, and manifestations of P-ACC for which an intervention was assessed in at least one randomized controlled trial (RCT). It is hoped this information will support investigators, policymakers, and prescribers navigate the flood of relevant data to ensure that management of P-ACC, at both the individual and population levels, is based on the best available knowledge. This resource will be continually updated as more research is released into the public space.

Summary of evidence

All odd numbered tables (Table ES1 to ES15) present RCTs according to the reported P- ACC related organ/system affected and indicate the primary outcome measures used for each investigation and the level of certainty. The even numbered tables (Table ES2

to ES16) summarize the status of evidence for the 37 potential therapeutic options for P- ACC for which studies were identified through this systematic review.

P-ACC-related asthenia or fatigue

Table ES1. List of RCTs on interventions for P-ACC-related asthenia or fatigue with primary outcome measures and certainty (n = 19)

Intervention		Overall number of studies including the intervention, n=19	HRQL improvement (n of studies)	Overall symptom improvement (n of studies)	Fatigue improvement (n of studies)	Functional capacity improvement (n of studies)	Strength improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Fermented food supplements		2		2					
Physical training		2	1		1	1	1		
tDCS	NEW	2	1		2			1	
1_MNA		1			1	1			
Actovegin		1			1				
ADAPT_232 (adaptogens)		1			1				
Arginine_Vitamin C		1			1		1		
Aromatherapy	NEW	1	1		1				
CQ10		1	1	1					
Cytoflavin		1			1				
Enzimes_Probiotics		1			1				
Hydrogen (nasal)		1			1	1			
Immunodaat	NEW	1	1		1				
Phytochemicals		1	1		1				
Leronlimab		1		1					
Telerehabilitation		1	1		1	1			

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table ES2. Summary of findings on potential therapeutic options for P-ACC-related asthenia or fatigue (n=16), as of 29 March 2023

	Intervention	Summary of findings
1	**1-MNA**	Uncertainty in potential benefits and harms. Further research is needed.
2	**Actovegin**	Actovegin may improve fatigue. However, certainty of the evidence was low. Further research is needed.
3	**ADAPT-232 (adaptogens)**	ADAPT-232 may not improve fatigue. However, certainty of the evidence was low. Further research is needed.
4	**Arginine + Vitamin C**	Uncertainty in potential benefits and harms. Further research is needed.
5	**Aromatherapy**	Uncertainty in potential benefits and harms. Further research is needed.
6	**Coenzyme Q10**	Uncertainty in potential benefits and harms. Further research is needed.
7	**Cytoflavin**	Cytoflavin may not improve fatigue. However, certainty of the evidence was low. Further research is needed.
8	**Enzymes + probiotics**	Enzymes + probiotics may improve fatigue. However, certainty of the evidence was low. Further research is needed.
9	**Fermented food supplements**	Uncertainty in potential benefits and harms. Further research is needed.
10	**Hydrogen (nasal)**	Uncertainty in potential benefits and harms. Further research is needed.
11	**Immunodaat**	Uncertainty in potential benefits and harms. Further research is needed.
12	**Leronlimab**	Uncertainty in potential benefits and harms. Further research is needed.
13	**Phytochemicals**	Phytochemicals may improve fatigue and HRQL. However, certainty of the evidence was low. Further research is needed.
14	**Physical training**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
15	**Transcranial direct current stimulation (tDCS)**	tDCS may improve fatigue and HRQL, and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.
16	**Telerehabilitation**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined 16 therapeutic options for P-ACC-related asthenia or fatigue.

• **Actovegin:** The results of one RCT suggest that actovegin may improve fatigue. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **ADAPT-232 (adaptogens):** The results of one RCT suggest that ADAPT-232 may not improve fatigue. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Cytoflavin:** The results of one RCT suggest that cytoflavin may not improve fatigue. However, certainty of the evidence was low because of imprecision and risk of bias. Further research is needed.

• **Enzymes + probiotics:** The results of one RCT suggest that enzymes + probiotics may not improve fatigue. However, certainty of the evidence was low because of imprecision and risk of bias. Further research is needed.

• **Transcranial direct current stimulation (tDCS):** The results of two RCTs suggest that tDCS may improve fatigue and HRQL and may not increase adverse events. However, certainty of the evidence was low because of imprecision. Further research is needed.

P-ACC-related dyspnea

Table ES3. List of RCTs of interventions for P-ACC-related dyspnea with primary outcome measures and certainty (n = 10)

Intervention		Overall number of studies including the intervention, n=10	HRQL improvement (n of studies)	Dyspnea improvement (n of studies)	Functional capacity improvement (n of studies)	Pulmonary function improvement (n of studies)	Radiological response (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Respiratory training	NEW	6	3	4		3			
ADAPT_232 (adaptogens)		1		1					
High dose steroids		1		1			1	1	1
Nebivolol	NEW	1		1					
Treamid		1		1	1	1		1	

Table ES4. Summary of findings on potential therapeutic options for P-ACC-related dyspnea (n=5), as of 29 March 2023

	Intervention	Summary of findings
1	**ADAPT-232 (adaptogens)**	ADAPT-232 may not improve dyspnea. However, certainty of the evidence was low. Further research is needed.
2	**High dose steroids**	High dose steroids, compared to standard dose steroids, may not improve dyspnea and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.
3	**Nebivolol**	Uncertainty in potential benefits and harms. Further research is needed.
4	**Respiratory training/rehabilitation**	Respiratory training/rehabilitation probably improves HRQL and may improve dyspnea. Further research is needed.
5	**Treamid**	Treamid may improve dyspnea and pulmonary function but may not improve functional capacity. Treamid may increase adverse events. However, certainty of the evidence was low. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined five therapeutic options for P-ACC-related dyspnea.

• **ADAPT-232 (adaptogens):** The results of one RCT suggest that ADAPT-232 may not improve dyspnea. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **High dose steroids:** The results of one RCT suggest that high dose steroids (prednisone 40 mg a day) may not improve dyspnea compared to standard dose steroids (prednisone 10 mg a day). However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

• **Respiratory training/rehabilitation:** The results of five RCTs suggest that respiratory training probably improves HRQL and may improve dyspnea. However, certainty of the evidence for dyspnea was low because of inconsistency and risk of bias. Further research is needed.

• **Treamid:** The results of one RCT suggest that treamid may improve dyspnea and pulmonary function but may not improve functional capacity. However, certainty of the evidence was low because of imprecision. Further research is needed.

P-ACC-related neurocognitive symptoms

Table ES5. List of RCTs of interventions for P-ACC-related neurocognitive symptoms with primary outcome measures and certainty (n=4)

Intervention		Overall number of studies including the intervention, n=4	HRQL improvement (n of studies)	Overall symptom improvement (n of studies)	Cognitive improvement (n of studies)	Depression improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Actovegin	NEW	1			1			
HBO		1	1		1	1		
taVNS		1						
tDCS		1			1			

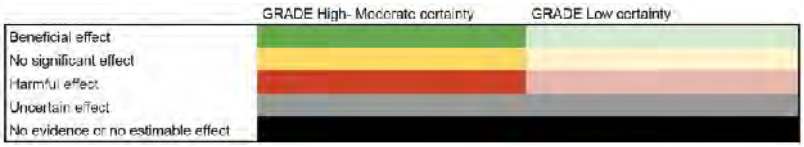


Table ES6. Summary of findings on potential therapeutic options for P-ACC-related neurocognitive symptoms (n=4), as of 29 March 2023

	Intervention	Summary of findings
1	**Actovegin**	Actovegin may improve cognition. However, certainty of the evidence was low. Further research is needed.
2	**Hyperbaric oxygen (HBO)**	HBO may improve HRQL. However, certainty of the evidence was low. Further research is needed.
3	**Transcutaneous auricular vagus nerve stimulation (taVNS)**	Uncertainty in potential benefits and harms. Further research is needed.
4	**Transcranial direct current stimulation (tDCS)**	tCDS may not improve cognition. However, certainty of the evidence was low. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of

clinical trials and observational studies. In this review, we identified and examined three therapeutic options for PCC neurocognitive symptoms.

• **Actovegin:** The results of one RCT suggest that actovegin may improve cognition. However, certainty of the evidence was low because of risk of bias. Further research is needed.

• **Hyperbaric oxygen (HBO):** The results of one RCT suggest that HBO may improve HRQL. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Transcranial direct current stimulation (tDCS):** The results of one RCT suggest that tDCS may not improve cognition. However, certainty of the evidence was low because of imprecision. Further research is needed.

P-ACC-related olfactory and/or gustatory dysfunction

Table ES7. List of RCTs of interventions for P-ACC-related olfactory and/or gustatory dysfunction with primary outcome measures and certainty (n=9)

Intervention		Overall number of studies including the intervention, n=9	HRQL improvement (n of studies)	Overall symptom improvement (n of studies)	Olfactory symptoms improvement (n of studies)	Gustatory symptoms improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Olfactory training		3			3			
Steroids	NEW	2			2	1		
ADAPT_232 (adaptogens)		1			1			
Palmitoylethanolamide_Luteolin		1			1			
Steroids (nasal)		1			1			
Theophylline_nasal	NEW	1	1		1		1	

Table ES8. Summary of findings on potential therapeutic options for P-ACC-related olfactory and/or gustatory dysfunction (n=6), as of 29 March 2023

	Intervention	Summary of findings
1	**ADAPT-232 (adaptogens)**	ADAPT-232 may not improve olfactory symptoms. However, certainty of the evidence was low. Further research is needed.
2	**Olfactory training**	Uncertainty in potential benefits and harms. Further research is needed.
3	**Palmitoylethanolamide + Luteolin**	Palmitoylethanolamide + Luteolin may not improve olfactory symptoms. However, certainty of the evidence was low. Further research is needed.
4	**Steroids (nasal)**	Uncertainty in potential benefits and harms. Further research is needed.
5	**Steroids**	Steroids may nor improve olfactory nor gustatory symptoms. Further research is needed.
6	**Theophylline (nasal)**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined five therapeutic options for PCC olfactory and/or gustatory dysfunction.

• **ADAPT-232 (adaptogens):** The results of one RCT suggest that ADAPT-232 may improve olfactory symptoms. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Palmitoylethanolamide + Luteolin:** The results of one RCT suggest that Palmitoylethanolamide + Luteolin may not improve olfactory symptoms. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Steroids:** The results of two RCTs suggest that steroids may not improve olfactory nor gustatory symptoms. However, certainty of the evidence was low because of imprecision. Further research is needed.

P-ACC-related cardiovascular system symptoms

Table ES9. List of RCTs of interventions for P-ACC-related cardiovascular system symptoms with primary outcome measures and certainty (n=1)

Intervention	Overall number of studies including the intervention, n=1	HRQL improvement (n of studies)	Overall symptom improvement (n of studies)	Tachycardia improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Ivabradine	1			1		

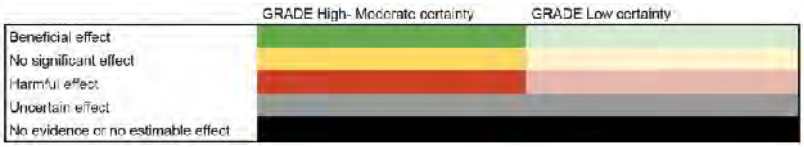


Table ES10. Summary of findings on potential therapeutic options for P-ACC-related cardiovascular system symptoms (n=1), as of 29 March 2023

	Intervention	Summary of findings
1	**Ivabradine**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined one therapeutic option for P-ACC- related cardiovascular system symptoms.

• **The effects of assessed interventions are uncertain.**

P-ACC-related psychological distress

Table ES11. List of RCTs of interventions for P-ACC-related psychological distress with primary outcome measures and certainty (n=1)

Intervention	Overall number of studies including the intervention, n=1	HRQL improvement (n of studies)	Depression improvement (n of studies)	Post traumatic stress disorder improvement (n of studies)	Psychologic distress improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Virtual reality info	1		1	1	1		

Table ES12. Summary of findings on potential therapeutic options for PCC psychological distress (n=1), as of 29 March 2023

	Intervention	Summary of findings
1	**Virtual reality informational video**	Virtual reality informational video may improve depression, post-traumatic stress, and psychological distress. However, certainty of the evidence was low. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined one therapeutic option for PCC psychological distress.

• **Virtual reality informational video:** The results of one RCT suggest that Virtual reality informational video may improve depression, post-traumatic stress, and psychological distress. However, certainty of the evidence was low because of imprecision. Further research is needed.

P-ACC-related thromboembolic risk

Table ES13. List of RCTs of interventions for P-ACC-related thromboembolic risk with primary outcome measures and certainty (n=1)

Intervention	Overall number of studies including the intervention, n=1	Mortality (n of studies)	HRQL improvement (n of studies)	VTE (symptomatic) (n of studies)	Major bleeding (n of studies)	Severe adverse events (n of studies)
Anticoagulants_Proph	1	1		1		

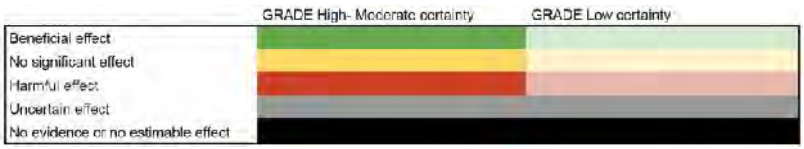


Table ES14. Summary of findings on potential therapeutic options for PCC thromboembolic risk (n=1), as of 29 March 2023

	Intervention	Summary of findings
1	**Anticoagulants (prophylactic dose)**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined one therapeutic option for PCC olfactory and/or gustatory dysfunction.

• **The effects of assessed interventions are uncertain.**

Pediatric inflammatory multisystem syndrome associated with SARS-CoV-2 (PIMS-TS)

Table ES13. List of RCTs of interventions for PIMS-TS with primary outcome measures and certainty (n=1)

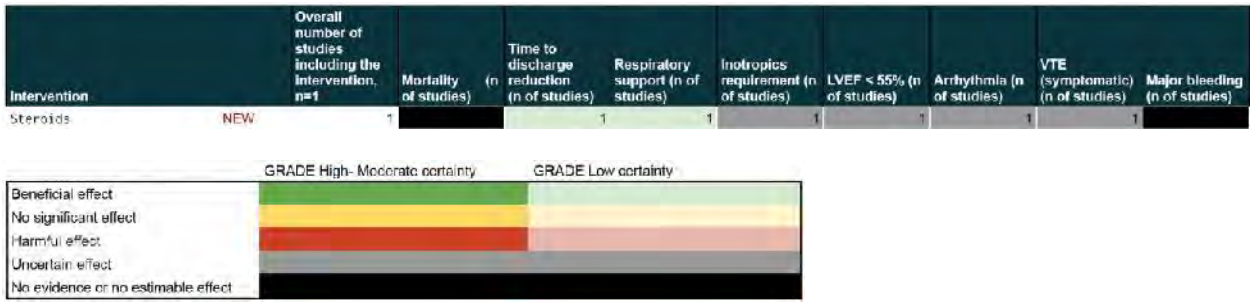


Table ES14. Summary of findings on potential therapeutic options for PCC thromboembolic risk (n=1), as of 29 March 2023

	Intervention	Summary of findings
1	**Steroids**	Steroids may reduce time to discharge and respiratory support requirements. However, certainty of the evidence was low for risk of bias and imprecision. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined one therapeutic option for PCC olfactory and/or gustatory dysfunction.

• **Steroids:** The results of one RCT suggest that steroids may reduce time to discharge and respiratory support requirements. However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

P-ACC prophylaxis

Table ES15. List of RCTs of interventions for P-ACC prophylaxis with primary outcome measures and certainty (n=5)

Intervention		Overall number of studies including the intervention, n=5	Mortality (n of studies)	HRQL improvement (n of studies)	P-ACC (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
CP	NEW	1			1		
Fluvoxamine	NEW	1			1		
Ivermectin	NEW	1			1		
Metformin	NEW	1			1		
Remdesivir	NEW	1	1		1		

Table ES16. Summary of findings on potential therapeutic options for P-ACC prophylaxis (n=5), as of 29 March 2023

	Intervention	Summary of findings
1	**Convalescent plasma**	Convalescent plasma may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.
2	**Fluvoxamine**	Uncertainty in potential benefits and harms. Further research is needed.
3	**Ivermectine**	Ivermectin may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.
4	**Metformin**	Metformin may reduce P-ACC. However, certainty of the evidence was low. Further research is needed.
5	**Remdesivir**	Remdesivir may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined one therapeutic option for PCC olfactory and/or gustatory dysfunction.

• **Metformin:** The results of one RCT suggest that metformin may reduce P-ACC. However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

• **Ivermectin:** The results of one RCT suggest that ivermectin may reduce P-ACC. However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

• **Convalescent plasma:** The results of one RCT suggest that convalescent plasma may not reduce P-ACC. However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

• **Remdesivir:** The results of one RCT suggest that remdesivir may not reduce P-ACC. However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

Changes since previous edition

• **Metformin for P-ACC prophylaxis:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Ivermectin for P-ACC prophylaxis:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Fluvoxamine for P-ACC prophylaxis:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **tDCS for P-ACC related asthenia/fatigue:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Convalescent plasma for P-ACC prophylaxis:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Immunodaat for P-ACC related asthenia/fatigue:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Nebivolol for P-ACC related dyspnea:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Respiratory training/rehabilitation for P-ACC related dyspnea:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Remdesivir P-ACC prophylaxis:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Aromatherapy P-ACC related asthenia/fatigue:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Steroids for P-ACC-related olfactory and/or gustatory dysfunction:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Theophylline (nasal) for P-ACC-related olfactory and/or gustatory dysfunction:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

Concluding remarks

• The Pan American Health Organization (PAHO) is continually monitoring ongoing research on any possible therapeutic options. As evidence emerges, PAHO will immediately assess and update its position, particularly as it applies to any special population subgroups such as children, expectant mothers, and those with immune conditions.

• PAHO is also mindful of the emerging differential impact of PCC on ethnic and minority groups and is continuously seeking data that could help in mitigating excess risk of severe illness or death in minority subgroups. These groups are plagued by social and structural inequities that bring to bear a disproportionate burden of COVID-19 illness.

• The safety of the patient suffering from COVID-19 is a key priority to improve the quality of care in the provision of health services.

• Adequately designed and reported clinical trials are crucial for the practice of evidence-based medicine. Most of the research to date on PCC has very poor methodology that is hidden and very difficult to validate. Greater transparency and better designed studies are urgently needed.

Systematic review of therapeutic options for post acute or post COVID-19 condition (P-ACC)

Background

Post COVID-19 condition (PCC), also known as long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC), is the continuation or development of new symptoms in the period after acute infection with SARS-CoV-2 *(1–4)*. The World Health Organization (WHO) definition of PCC states that these symptoms should be present after three months of the initial SARS-CoV-2 infection and last for at least two months with no other explanation *(1, 2)*. While PASC definitions states persistent or new symptoms need to be present 30 days after a documented SARS-COV-2 infection or the onset of COVID-19 symptoms (*3, 4*). Post COVID-19 condition or post-acute sequelae of SARS-CoV-2 infection (P-ACC) can affect anyone exposed to SARS-CoV-2, regardless of age or severity of acute infection. Many of the reported symptoms are debilitating and have a strong negative impact on mental health and the quality of life *(5)*. While most patients recover, some may experience multiple outcomes, with multiple organ systems affected simultaneously, including cardiovascular, mental, metabolic, renal, and others *(3, 6)*. Recommendations for the management of patients with PCC are continuously being developed and need to evolve as evidence of interventions effects becomes available (*7*).

In this review, we compiled the following evidence on potential therapeutic options for P- ACC. We included all the identified clinical forms, symptoms, and manifestations of P- ACC for which an intervention was assessed in at least one randomized controlled trial (RCT). We hope this information will support investigators, policymakers, and prescribers navigate the flood of relevant data to ensure that management of P-ACC, at both the individual and population levels, is based on the best available knowledge. We will endeavor to continually update this resource as more research is released into the public space.

Methods

We used the Living OVerview of Evidence (L·OVE; available from: https://iloveevidence.com) platform to identify studies for inclusion in this review. This platform is a system that maps PICO (Patient–Intervention–Comparison–Outcome) questions to a repository developed by Epistemonikos Foundation. This repository is continuously updated through searches in electronic databases, preprint servers, trial registries, and other resources relevant to COVID-19. The latest version of the methods, the total number of sources screened, and a living flow diagram and report of the project is updated regularly on the L·OVE website *(8)*.

Search strategy

We systematically searched in L·OVE for COVID-19. The search terms and databases covered are described on the L·OVE search strategy methods page (available from: https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?question_domain=undefined&section=methods). The repository is continuously updated, and the information is transmitted in real time to the L·OVE platform. It was last checked for this review on 29 March 2023. The searches covered the period from the inception date of each database, and no study design, publication status, or language restriction was applied.

Study selection

The results of the searches in the individual sources were de-duplicated by an algorithm that compares unique identifiers (database identification number, digital object identifier [DOI], trial registry identification number), and citation details (i.e., author names, journal, year of publication, volume, number, pages, article title, and article abstract). Then, the information matching the search strategy was sent in real time to the L·OVE platform, where at least two authors independently screened the titles and abstracts yielded against the inclusion criteria. We obtained the full reports for all titles that appeared to meet the inclusion criteria or required further analysis and then decided about their inclusion.

Inclusion criteria

We aimed to find all available RCTs for potential therapeutic interventions for P-ACC with study designs that included head-to-head comparisons, or control groups with no intervention or a placebo. Target patient populations included both adults and children with persistent, or new, symptoms or clinical manifestations after acute COVID-19. We used the term Post Acute or Post COVID-19 condition (P-ACC) to refer to the population included in our review (studies reporting on patients with persistent or new symptoms after acute COVID-19 independently of the time of onset of those symptoms)*(1–4)*. We focused on comparative effectiveness studies that provide evidence on outcomes of crucial importance to patients (mortality, health-related quality of life [HRQL], and disease-specific symptoms).

Living evidence synthesis

An artificial intelligence algorithm deployed in the Coronavirus/COVID-19 topic of the L·OVE platform provides instant notification of articles with a high likelihood of being eligible. The authors review them, decide upon inclusion, and update the living web version of the review accordingly. If meta-analytical pooling is possible from retrieved evidence, we will do this to derive more precise estimates of effect and derive additional statistical power. No electronic database search restrictions were imposed.

For any meta-analytical pooling, if and when data allow, we pool all studies and present the combined analysis with relative and absolute effect sizes. To assess interventions' absolute effects, we applied relative effects to baseline risks (risks with no intervention). For baseline risks we used the mean risk in the control groups from included RCTs. For continuous outcomes, when possible, we calculated relative and absolute effects by estimating the proportion of patients with important improvement or deterioration following published guidance *(9)*.

For result interpretations and imprecision assessment we used a minimally contextualized approach that considers whether the 95% confidence interval (CI) includes the null effect, or, when the point estimate is close to the null effect, whether the 95% CI lies within the

boundaries of small but important benefit and harm that corresponds to every outcome assessed *(10, 11)*.

We used the following absolute effects thresholds to define important benefits and harms: Mortality, +/-1%; HRQL improvement, +/-2%; Overall symptom improvement, +/-5%; Functional capacity improvement, +/-5%; Strength improvement, +/-5%; Fatigue improvement, +/-5%; Pulmonary function improvement, +/-10%; Radiological response, +/-10%; Cognitive improvement, +/-5%; Depression improvement, +/-5%; Olfactory symptoms improvement, +/-5%; Gustatory symptoms improvement, +/-5%; Tachycardia improvement, +/-5%; Venous thromboembolism (VTE) (symptomatic), +/-3%; Post-traumatic stress disorder improvement, +/-5%; Psychological distress improvement, +/-5%; Major bleeding, +/-3%; Severe adverse events, +/-3%; Adverse events, +/-5%; Time to discharge reduction, +/-4%; Respiratory support requirement +/-2%; Inotropic requirement +/-2%; Left ventricular ejection fraction deterioration (LVEF <55%) +/-5%; Arrhythmia +/-5%; P-ACC, +/-3%.

For some interventions when we found significant heterogeneity, we performed subgroup analysis considering: 1) risk of bias (high/moderate vs low risk of bias); and 2) intervention characteristics (e.g., different doses or administration schemes). When we observed significant differences between subgroups, we presented individual subgroups' estimates of effect and certainty of the evidence assessment.

A risk of bias assessment was applied to RCTs focusing on randomization, allocation concealment, blinding, attrition, or other biases relevant to the estimates of effect (Table 1) *(12)*. The GRADE approach was used to assess the certainty of the body of evidence for every comparison on an outcome basis *(13)*.

Study selection, data extraction, and risk of bias assessment were performed, independently and in parallel, by two reviewers. Discrepancies were resolved by discussion.

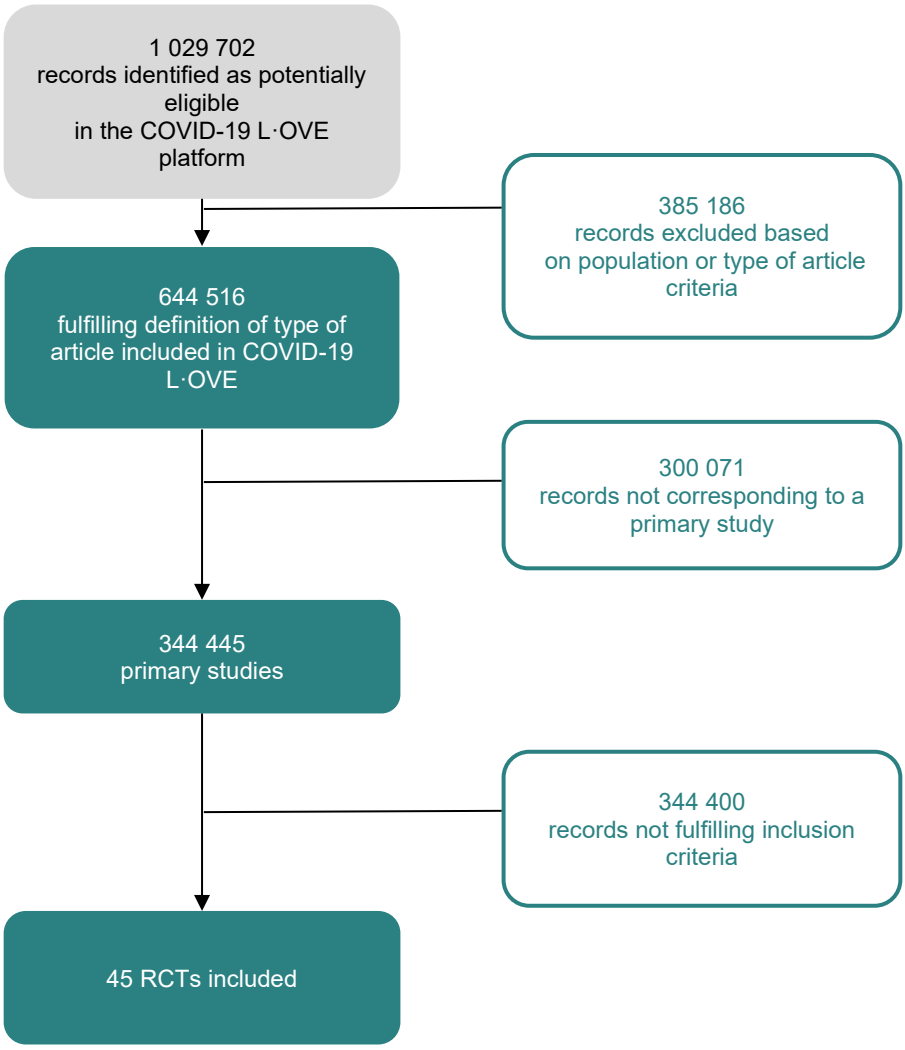
We used MAGIC authoring and publication platform (available from: https://app.magicapp.org/) to generate the tables summarizing our findings, which are included in Annex 1.

Results

Studies identified and included

The study identification and selection process is shown in Figure 1. A total of 45 RCTs were selected for inclusion. A list of excluded studies is available upon request.

Figure 1. Study identification and selection process



Risk of bias

Overall, our risk of bias assessment for the limited reported RCTs found high risk of bias due to suboptimal randomization, allocation concealment, and blinding (as well as other methodological and reporting concerns). Most RCTs were also very small in size and had small event numbers. The methods were very poor overall, and the reporting was suboptimal. In general, follow-up was short. The risk of bias assessment of each RCT is presented in Table 1.

Table 1. Risk of bias of included RCTs

Study	Risk-of-bias arising from randomization process	Risk-of-bias due to deviations from the intended interventions	Risk-of-bias due to missing outcome data	Risk-of-bias in measurement of the outcome	Risk-of-bias in selection of the reported result	Overall Risk-of-bias judgement	
						Mortality	HRQL, symptom specific outcomes
Vaira LA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RC 4-7-2020 (Abdelalim AA et al)	High	Some Concerns	Low	Some Concerns	Low	High	High
Di Stadio	Low	Low	Low	Low	Low	Low	Low
Chudzik M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CITADEL	High	Some Concerns	Low	Some Concerns	Low	High	High
MICHELLE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Zilberman-Itskovich	Low	Low	Low	Low	Low	Low	Low
Botek M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Jadhav KP et al	High	Some Concerns	Low	Some Concerns	Low	High	High
COLDSTER	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Oliver-Mas	Low	Low	Low	Low	Low	Low	Low
Nambi	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Di Stadio_2	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hansen	Low	Low	Low	Low	Low	Low	Low
Tosato	High	Some Concerns	Low	Some Concerns	Low	High	High
Rathi	High	Some Concerns	Low	Some Concerns	Low	High	High
Bazdyrev	Low	Low	Low	Low	Low	Low	Low
King	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ICU-VR	High	Some Concerns	Low	Some Concerns	Low	High	High
ENO Breathe	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Pires	High	Some Concerns	Low	Some Concerns	Low	High	High
McNarry	High	Some Concerns	Low	Some Concerns	Low	High	High
Srinivasan	High	Some Concerns	Low	Some Concerns	Low	High	High
Kharaeva_Moderate	High	Some Concerns	Low	Some Concerns	Low	High	High
Kharaeva_Severe	High	Some Concerns	Low	Some Concerns	Low	High	High
Gaylis	High	Some Concerns	Low	Some Concerns	Low	High	High
Karosanidze	Low	Low	Low	Low	Low	Low	Low
Badran	Low	Low	Low	Low	Low	Low	Low
COVANOS	Low	Some Concerns	Low	Some Concerns	Low	Low	High
RECOVER	High	Some Concerns	Low	Some Concerns	Low	High	High
Kutasov	High	Some Concerns	Low	Some Concerns	Low	High	High
Vallier	High	Some Concerns	Low	Some Concerns	Low	High	High
Swissped RECOVERY	Low	Some Concerns	Low	Some Concerns	Low	Low	High
UK Phyto-V	High	Some Concerns	Low	Some Concerns	Low	High	High
Rodriguez-Blanco	High	Some Concerns	Low	Some Concerns	Low	High	High
COVID-OUT - Metformin	Low	Low	High	Low	Low	High	High
COVID-OUT - Ivermectin	Low	Low	High	Low	Low	High	High
COVID-OUT - Fluvoxamine	Low	Low	High	Low	Low	High	High
Santana	Low	Low	Low	Low	Low	Low	Low
CSSC-004	Low	Low	Some Concerns	Low	Low	Low	Some Concerns
Deshpande	High	Some Concerns	Low	Some Concerns	Low	High	High
Dal Negro	High	Some Concerns	Low	Some Concerns	Low	High	High
InsCOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Rutkowski	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SOLIDARITY - Finland	Low	Low	Low	Low	Low	Low	Low
Hawkins	Low	Low	Low	Low	Low	Low	Low
Schepens	Low	Low	Low	Low	Low	Low	Low
Kusumawardani	High	Some Concerns	Low	Some Concerns	Low	High	High
SCENT2	Low	Low	Low	Low	Low	Low	Low

Main findings

P-ACC-related asthenia or fatigue

Actovegin

See Summary of findings Table A1, Annex 1

We identified one RCT including 444 participants in which Actovegin was compared against standard of care. Our results showed:

- Actovegin may improve fatigue, relative risk (RR) 1.84 (95% CI 1.59 to 2.14); risk difference (RD) 39.7% (95% CI 27.7% to 56.3%); Low certainty ⊕⊕◯◯

ADAPT-232 (adaptogens)

See Summary of findings Table A2, Annex 1

We identified one RCT including 99 participants in which ADAPT-232 was compared against standard of care. Our results showed:

- ADAPT-232 may not improve fatigue, relative risk (RR) 1.02 (95% CI 0.84 to 1.24); risk difference (RD) 1.6% (95% CI –12.6% to 18.9%); Low certainty ⊕⊕◯◯

Cytoflavin

See Summary of findings Table A3, Annex 1

We identified one RCT including 200 patients in which cytoflavin was compared against standard of care. Our results showed:

- Cytoflavin may not improve fatigue, RR 1.02 (95% CI 0.98 to 1.06); RD 2.1% (95% CI –1.9% to 6.2%); Low certainty ⊕⊕◯◯

Enzymes + probiotics

See Summary of findings Table A4, Annex 1

We identified one RCT including 200 patients in which enzymes + probiotics were compared against standard of care. Our results showed:

- Enzymes + probiotics may improve fatigue, RR 6.07 (95% CI 3.79 to 9.71); RD 76% (95% CI 41.8% to 85%); Low certainty ⊕⊕◯◯

Phytochemicals

See Summary of findings Table A5, Annex 1

We identified one RCT including 147 patients in which phytochemicals were compared against standard of care. Our results showed:

- Phytochemicals may improve HRQL, RR 1.33 (95% CI 1.03 to 1.71); RD 18% (95% CI 1.8% to 39%); Low certainty ⊕⊕◯◯
- Phytochemicals may improve fatigue, RR 1.24 (95% CI 0.95 to 1.62); RD 13.1% (95% CI -2.5% to 33.5%); Low certainty ⊕⊕◯◯

Transcranial direct current stimulation (tDCS)

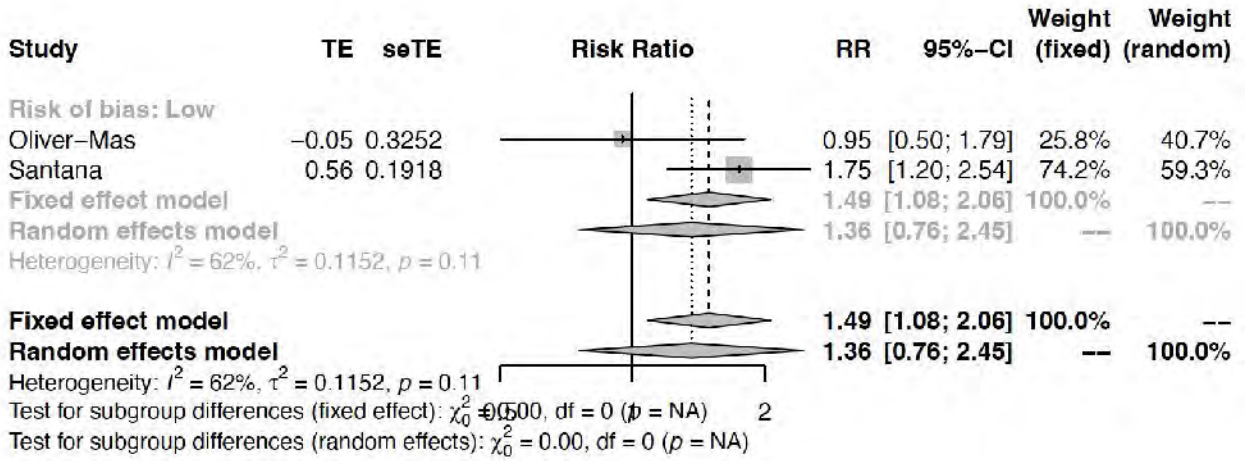
See Summary of findings Table A6, Annex 1

We identified two RCT including 117 patients in which tDCS was compared against standard of care. Our results showed:

- tDCS may improve fatigue, RR 1.36 (95% CI 0.76 to 2.45); RD –16.9% (95% CI –11.2% to 53%); Low certainty ⊕⊕◯◯ (see figure 2.)

- tDCS may improve HRQL, RR 1.37 (95% CI 1.09 to 1.71); RD –26% (95% CI –6.7% to 30%); Low certainty ⊕⊕◯◯

Figure 2. Fatigue in RCTs comparing tDCS with standard of care for treatment of patients with P-ACC-related asthenia/fatigue



P-ACC-related dyspnea

ADAPT-232 (adaptogens)

See summary of findings Table A7 in Annex 1

We identified one RCT including 99 patients in which ADAPT-232 was compared against standard of care. Our results showed:

- ADAPT-232 may not improve dyspnea, RR 1 (95% CI 0.94 to 1.06); RD 0% (95% CI –5.4% to 5.7%); Low certainty ⊕⊕◯◯

High dose steroids

See Summary of findings Table A9, Annex 1

We identified one RCT including 130 patients in which high dose steroids (prednisone 40 mg a day) was compared against standard dose steroids (prednisone 10 mg a day). Our results showed:

- High dose steroids may not improve dyspnea, RR 1 (95% CI 0.87 to 1.15); RD 0% (95% CI –11% to 13%); Low certainty ⊕⊕◯◯
- High dose steroids may not increase adverse events, RR 0.92 (95% CI 0.75 to 1.13); RD –6.2% (95% CI –19.3% to 10%); Low certainty ⊕⊕◯◯

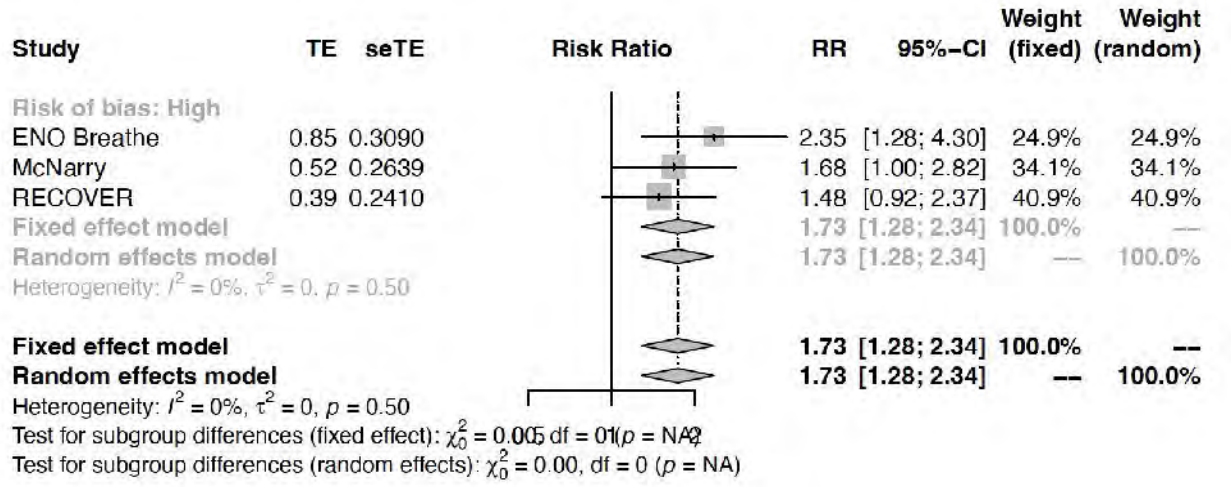
Respiratory training/rehabilitation

See Summary of findings Table A10, Annex 1

We identified five RCTs including 337 patients in which different modalities of respiratory training/rehabilitation were compared with standard of care. In addition, we identified one study that compared home based respiratory training vs. inpatient respiratory training, one study comparing VR respiratory training vs. conventional respiratory training and one study that compares incentive spirometry vs. conventional respiratory training. Our results showed:

- Respiratory training/rehabilitation may improve HRQL, RR 1.73 (95% CI 1.28 to 2.34); RD 25.5% (95% CI 9.8% to 46.7%); Moderate certainty ⊕⊕⊕◯ (see Figure 3)
- Respiratory training/rehabilitation may improve dyspnea, RR 1.88 (95% CI 1.43 to 2.47); RD 22.9% (95% CI 10.1% to 39.7%); Low certainty ⊕⊕◯◯

Figure 3. HRQL in RCTs comparing respiratory training/rehabilitation with standard of care for treatment of patients with P-ACC-related dyspnea.



Treamid

See Summary of findings Table A11, Annex 1

We identified one RCT including 59 patients in which treamid was compared with standard of care. Our results showed:

- Treamid may improve dyspnea, RR 1.96 (95% CI 0.9 to 4.25); RD 21.7% (95% CI –2.3% to 73.7%); Low certainty ⊕⊕◯◯
- Treamid may improve functional capacity, RR 1.1 (95% CI 0.64 to 1.9); RD 0.4% (95% CI 16.2% to 39.8%); Low certainty ⊕⊕◯◯

- Treamid may increase adverse events, RR 1.19 (95% CI 0.56 to 2.5); RD 5.5% (95% CI –12.7% to 43.6%); Low certainty ⊕⊕◯◯

P-ACC-related neurocognitive symptoms

Actovegin

See Summary of findings Table A12, Annex 1

We identified one RCT including 44 patients in which actovegin was compared with standard of care. Our results showed:

- Actovegin may improve cognition, RR 1.19 (95% CI 1.06 to 1.33); RD 12.7% (95% CI 4.2% to 22.3%); Low certainty ⊕⊕◯◯

Hyperbaric oxygen (HBO)

See Summary of findings Table A13, Annex 1

We identified one RCT including 73 patients in which HBO was compared with standard of care. Our results showed:

- HBO may improve HRQL, RR 1.3 (95% CI 0.84 to 2); RD 13.9% (95% CI –7.4% to 46.9%); Low certainty ⊕⊕◯◯

Transcranial direct current stimulation (tDCS)

See Summary of findings Table A14, Annex 1

We identified one RCT including 47 patients in which tDCS was compared with standard of care. Our results showed:

- tDCS may not improve HRQL, RR 0.59 (95% CI 0.33 to 1.05); RD –27.5% (95% CI –44.8% to 3.4%); Low certainty ⊕⊕◯◯

P-ACC-related olfactory and/or gustatory dysfunction

ADAPT-232 (adaptogens)

See Summary of findings Table A15, Annex 1

We identified one RCT including 99 patients in which ADAPT-232 was compared with standard of care. Our results showed:

- ADAPT-232 may not improve olfactory symptoms, RR 0.89 (95% CI 0.79 to 1.01); RD –10.3% (95% CI –20.5% to 1.4%); Low certainty ⊕⊕◯◯

Palmitoylethanolamide + Luteolin

See Summary of findings Table A16, Annex 1

We identified one RCT including 126 patients in which palmitoylethanolamide + luteolin was compared with standard of care. Our results showed:

- Palmitoylethanolamide + luteolin may not improve olfactory symptoms, RR 1.11 (95% CI 0.68 to 1.81); RD 4.1% (95% CI –11.7% to 29.7%); Low certainty ⊕⊕◯◯

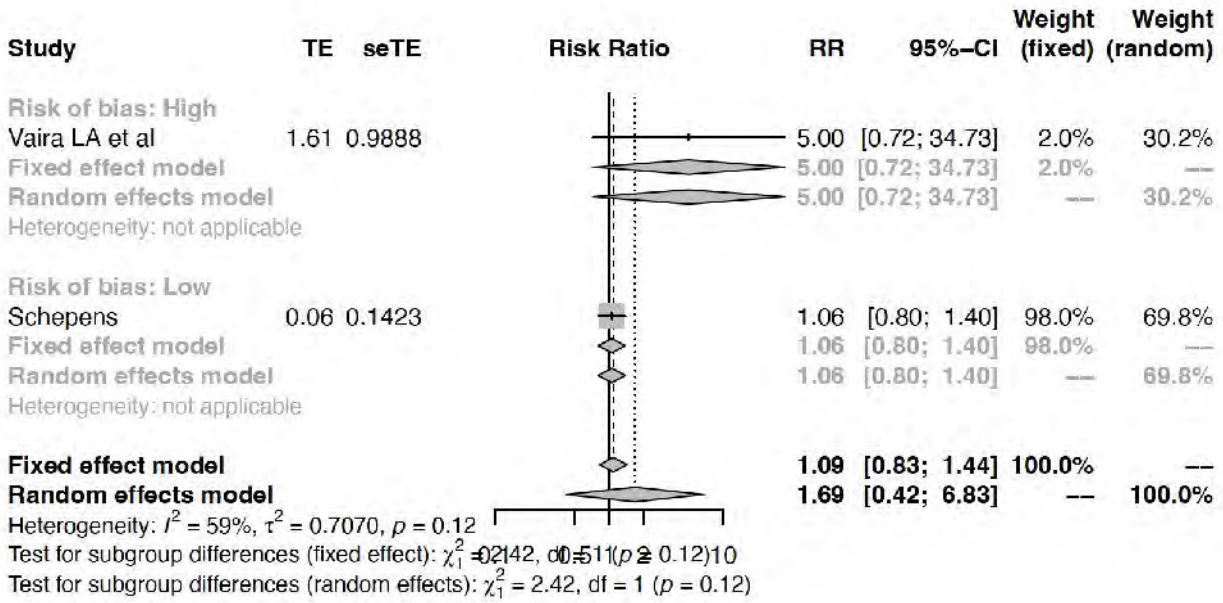
Steroids

See Summary of findings Table A17, Annex 1

We identified two RCT including 131 patients in which steroids were compared with standard of care. Our results showed:

- Steroids may not improve olfactory symptoms, RR 1.09 (95% CI 0.83 to 1.44); RD 3.3% (95% CI –6.2% to 16.1%); Low certainty ⊕⊕◯◯ (figure 4)
- Steroids may not improve gustatory symptoms, RR 1.01 (95% CI 0.67 to 1.53); RD 0.5% (95% CI –14.6% to 23.3%); Low certainty ⊕⊕◯◯

Figure 4. Olfactory symptoms in RCTs comparing steroids with standard of care for treatment of patients with P-ACC-related olfactory and/or gustatory dysfunction.


Study
TE
seTE
Risk Ratio
RR
95%–CI
Weight (fixed)
Weight (random)
Risk of bias: High
Vaira LA et al 1.61 0.9888 5.00 [0.72; 34.73] 2.0% 30.2%
Fixed effect model 5.00 [0.72; 34.73] 2.0% –
Random effects model 5.00 [0.72; 34.73] – 30.2%
Heterogeneity: not applicable
Risk of bias: Low
Schepens 0.06 0.1423 1.06 [0.80; 1.40] 98.0% 69.8%
Fixed effect model 1.06 [0.80; 1.40] 98.0% –
Random effects model 1.06 [0.80; 1.40] – 69.8%
Heterogeneity: not applicable
Fixed effect model 1.09 [0.83; 1.44] 100.0% –
Random effects model 1.69 [0.42; 6.83] – 100.0%
Heterogeneity: I^2 = 59%, τ^2 = 0.7070, p = 0.12
Test for subgroup differences (fixed effect): χ^2_1 = 2.42, df = 1 (p = 0.12)
Test for subgroup differences (random effects): χ^2_1 = 2.42, df = 1 (p = 0.12)

P-ACC-related cardiovascular system symptoms

The effects of the assessed interventions are uncertain.

P-ACC-related psychological distress

Virtual reality (VR) informational video

See Summary of findings Table A18, Annex 1

We identified one RCT including 89 patients in which a virtual reality-based (VR) intervention was compared with standard of care. Our results showed:

- VR informational video may improve depression, RR 1.21 (95% CI 0.95 to 1.54); RD 14% (95% CI –3.7% to 36.7%); Low certainty ⊕⊕◯◯
- VR informational video may improve post-traumatic stress, RR 1.18 (95% CI 0.98 to 1.42); RD 13.8% (95% CI –1.5% to 32.3%); Low certainty ⊕⊕◯◯
- VR informational video may improve psychological distress, RR 1.49 (95% CI 1.08 to 2.05); RD 25.5% (95% CI 4.1% to 55.1%); Low certainty ⊕⊕◯◯

P-ACC-related thromboembolic risk

The effects of the assessed interventions are uncertain.

Pediatric inflammatory multisystem syndrome associated with SARS-CoV-2 (PIMS-TS)

Steroids

See Summary of findings Table A19, Annex 1

We identified one RCT including 75 patients in which systemic steroids were compared with intravenous immunoglobulins (IVIG). Our results showed:

- Steroids may reduce time to discharge, RR 1.09 (95% CI 0.88 to 1.39); RD 4.5% (95% CI -6% to 19.5%); Low certainty ⊕⊕◯◯
- Steroids may reduce respiratory support requirements, RR 0.49 (95% CI 0.27 to 0.89); RD -28.2% (95% CI -40.5% to -5.9%); Low certainty ⊕⊕◯◯

P-ACC prophylaxis

Metformin

See Summary of findings Table A20, Annex 1

We identified one RCT including 1125 patients in which metformin was compared with standard of care. Our results showed:

- Metformin may reduce P-ACC, RR 0.59 (95% CI 0.39 to 0.88); RD -4.3% (95% CI -6.4% to -1.2%); Low certainty ⊕⊕◯◯

Ivermectin

See Summary of findings Table A21, Annex 1

We identified one RCT including 739 patients in which metformin was compared with standard of care. Our results showed:

- Metformin may reduce P-ACC, RR 0.99 (95% CI 0.61 to 1.62); RD 0% (95% CI -1.7% to 2.6%); Low certainty ⊕⊕◯◯

Convalescent plasma

See Summary of findings Table A22, Annex 1

We identified one RCT including 882 patients in which metformin was compared with standard of care. Our results showed:

- Convalescent plasma may not reduce P-ACC, RR 0.93 (95% CI 0.77 to 1.12); RD -2.4% (95% CI -7.9% to -4.2%); Low certainty ⊕⊕◯◯

Remdesivir

See Summary of findings Table A23, Annex 1

We identified one RCT including 181 patients in which metformin was compared with standard of care. Our results showed:

- Remdesivir plasma may not reduce P-ACC, RR 1.06 (95% CI 0.53 to 2.13); RD 0.8% (95% CI -6.9% to -16.4%); Low certainty ⊕⊕◯◯

Full description of included studies

Tables 2 to 8 list all the identified studies that were included in this systematic review by intervention and P-ACC-related organ system affected. The treatments are arranged in alphabetical order. Study or author names, publication status, patient populations, interventions, sources of bias, outcomes, effect sizes, and certainty are listed for each study.

Table 2. Description of included studies and interventions effects for P-ACC-related asthenia or fatigue

1-MNA **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Chudzik et al. *(14)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 30 days of acute COVID-19). 25 assigned to 1-MNA 58 mg a day and 25 assigned to standard of care.	Median age 49.5, male 32%, hypertension 14%, diabetes 2%	Not reported (NR)	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Actovegin **Actovegin may improve fatigue. However, certainty of the evidence was low. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
Kutashov et al. (15); Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after NR days of acute COVID-19). 222 assigned to Actovegin 1200 mg a day for 60 days and 222 assigned to standard of care.	Mean age 67.6, male 31.98%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 1.84 (95% CI 1.59 to 2.14); RD 39.7% (95% CI 27.7.6% to 53.6%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

ADAPT-232 (adaptogens) ADAPT-232 may not improve fatigue. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Karosanidze et al. *(16)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 30 days of acute COVID-19). 49 assigned to ADAPT-232 (adaptogens) 60 mL a day for 14 days and 50 assigned to standard of care.	Mean age 48.9, male 14%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 1.02 (95% CI 0.84 to 1.24); RD 1.6% (95% CI –12.6% to 18.9%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Arginine + Vitamin C Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard**

	analyzed				**of care (SOC) and GRADE certainty of the evidence**
RCT					
Tosato et al. *(17)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 28 days of acute COVID-19). 23 assigned to Arginine + Vitamin C 1.66 g/500 mg for 28 days and 23 assigned to standard of care.	Mean age 50.5 ± 14, male 34.8%, interval between COVID-19 and enrolment 254 days, hospitalization during COVID-19 56.5%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** No information **Strength improvement:** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Severe adverse events:** No information
Aromatherapy **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					

Hawkins et al *(18)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 150 days of acute COVID-19). 20 assigned to Aromatherapy Twice a day for 14 days and 20 assigned to standard of care.	Male 0%	NR	Low risk of bias	**HRQL improvement:** Very low certainty ⨁◯◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⨁◯◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Coenzyme Q10 (CQ10) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Hansen et al. *(19)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 84 days of acute COVID-19). 59 assigned to coenzyme Q10 500 mg a day for 6 weeks and 60 assigned to standard of care.	Median age 49, male 25.2%, obesity 33.6%, interval between COVID-19 and enrolment 288.55 days, hospitalization during COVID-19 15.1%	NR	Low risk of bias	**HRQL improvement:** Very low certainty ⨁◯◯◯ **Overall symptom improvement:** Very low certainty ⨁◯◯◯ **Fatigue improvement:** No

					information **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Cytoflavin **Cytoflavin may not improve fatigue. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
CITADEL trial *(20)*, Putilina et al.; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 30 to 90 days of acute COVID-19). 50 assigned to cytoflavin 2 tablets a day for 25 days and 50 assigned to standard of care.	Mean age 40.4 ± 12, male 57%, hypertension 38%, diabetes 4%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 1.02 (95% CI 0.98 to 1.06); RD 2.1% (95% CI –1.9% to 6.2%); Low certainty ⊕⊕◯◯

					Functional capacity improvement: No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Enzymes + probiotics **Enzymes + probiotics may improve fatigue. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Rathi et al. *(21)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after acute COVID-19). 100 assigned to enzymes + probiotics ImmunoSEB (500 mg/capsule) + ProbioSEB CSC3 (5 billion CFUs /capsule) and 100 assigned to standard of care.	Mean age 41.2 ± 13, male 63.5%, interval between COVID-19 and enrolment 19.5 days, one comorbidity 14.5%	NR	High risk of bias Notes: Concealment of allocation and blinding probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 6.07 (95% CI 3.79 to 9.71); RD 76% (95% CI 41.8% to 85%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information

					Strength improvement: No information **Adverse events:** No information **Severe adverse events:** No information
Fermented food supplements **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Kharaeva et al. *(22)*; Peer reviewed; 2022	Patients with P-ACC after moderate infection (asthenia or fatigue after acute COVID-19). 68 assigned to fermented food supplements 14 g twice a day for 20 days and 29 assigned to standard of care.	Age 38–69, male 51.5%, hypertension 36.1%, diabetes 15.5%, chronic lung disease 14.4%, obesity 19.6%, hospitalization during COVID-19 46.4%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** Very low certainty ⨁◯◯◯ **Fatigue improvement:** No information **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Kharaeva et al. *(22)*; Peer reviewed; 2022	Patients with P-ACC after severe infection (asthenia or fatigue after 0 days of acute COVID-19). 64 assigned to fermented food supplements 14 g twice a day for 20 days and 27 assigned to standard of care.	Age 36–65, male 47.2%, diabetes 28.6%, chronic lung disease 20.9%, asthma 3.3%, chronic heart disease 37.5%, obesity 40.6%, hospitalization during COVID-19 41.8%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Hydrogen (nasal) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Botek et al. *(23)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 21 to 35 days of acute COVID-19). 26 assigned to hydrogen (nasal) 300 mL/min for 14 days and 24 assigned to standard of care.	Mean age 40, male 52%, interval between COVID-19 and enrolment 25 days	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Immunodaat **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Deshpande trial *(24)*; Preprint; 2022	Patients with post COVID-19 condition. 26 assigned to Immunodaat 500 mg a day for 30 days and 28 assigned to standard of care.	Mean age 38.9, male 59.4%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** Very low certainty ⊕◯◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information

					Severe adverse events: No information
Leronlimab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Gaylis et al. *(25)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 90 days of acute COVID-19). 27 assigned to Leronlimab 700 mg a week for 8 weeks and 26 assigned to standard of care.	NR	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** Very low certainty ⊕◯◯◯ **Fatigue improvement:** No information **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse**

					events: No information
Physical training **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Nambi et al. *(26)*; Peer reviewed; 2022	Patients with P-ACC (sarcopenia after acute COVID-19). 36 assigned to aerobic training (high intensity) and 37 assigned to aerobic training (standard intensity).	Mean age 63.5, male 100%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** Very low certainty ⊕◯◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Strength improvement:** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Severe adverse events:** No information
Rodriguez-Blanco et al; *(27)* Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 40 days of acute COVID-19). 24 assigned to endurance training rehabilitation (ETR) (10 breathing and strength-based exercises) for 14 days, and 24 assigned to standard of care.	Mean age 40.7, male 22.91%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Phytochemicals **Phytochemicals may improve fatigue and HRQL. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
UK Phyto-V trial; (28) Thomas et al; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after acute COVID-19). 74 assigned to phytochemicals one capsule a day and 73 assigned to standard of care.	Mean age 53, male 56%, obesity 35%, interval between COVID-19 and enrolment 108 days, hospitalization during COVID-19 63%	NR	High risk of bias Notes: Concealment of allocation and blinding probably inappropriate.	**HRQL improvement:** RR 1.33 (95% CI 1.03 to 1.71); RD 18% (95% CI 1.8% to 39%); Low certainty ⨁⨁◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** RR 1.24 (95% CI 0.95 to 1.62); RD 13.1% (95% CI -2.5% to 33.5%); Low certainty ⨁⨁◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Transcranial direct current stimulation (tDCS) tDCS may improve fatigue and HRQL, and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Oliver-Mas et al. *(29)*; Preprint; 2022	Patients with P-ACC (asthenia or fatigue after 180 days of acute COVID-19). 23 assigned to transcranial direct current stimulation (tDCS) 1 session a week for 8 weeks and 24 assigned to standard of care.	Mean age 45.6, male 21.3%, hypertension 12.8%, diabetes 4.3%, interval between COVID-19 and enrolment 620 days, hospitalization during COVID-19 14.9%	NR	Low risk of bias	**HRQL improvement:** RR 1.37 (95% CI 1.09 to 1.71); RD – 26% (95% CI – 6.7% to 30%); Low certainty ⊕⊕◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** RR 1.36 (95% CI 0.76 to 2.45); RD – 16.9% (95% CI – 11.2% to 53%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** RR 0.83 (95% CI 0.26 to 2.73); RD – 3.4% (95% CI – 15.5% to 36%); Low certainty ⊕⊕◯◯%) **Severe adverse events:** No information
Santana et al *(30);* Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 90 days of acute COVID-19). 35 assigned to transcranial direct current stimulation (tDCS) 10 sessions and 35 assigned to standard of care.	Mean age 53, male 35.7%, hypertension 17.1%, diabetes 14.3%, chronic lung disease 5.7%, CHD 7.1%, , hospitalization during COVID-19 25.7%	NR	Low risk of bias	

Telerehabilitation Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
King et al. *(31)*; Preprint; 2022	Patients with P-ACC (asthenia or fatigue after 110 days of acute COVID-19). 11 assigned to telerehabilitation twice weekly for 10 weeks and 10 assigned to standard of care.	Mean age 48.5 ± 13, male 47.6%, interval between COVID-19 and enrolment 366 days, hospitalization during COVID-19 19%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** Very low certainty ⊕◯◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Table 3. Description of included studies and interventions effects for P-ACC-related dyspnea

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
ADAPT-232 (adaptogens) **ADAPT-232 may not improve fatigue. However, certainty of the evidence was low. Further research is needed.**					
RCT					
Karosanidze et al. *(16)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 30 days of acute COVID-19). 49 assigned to ADAPT-232 (adaptogens) 60 mL a day for 14 days and 50 assigned to standard of care.	Mean age 48.9, male 14%	NR	Low risk of bias	**HRQL improvement:** No information **Dyspnea improvement:** RR 1. (95% CI 0.94 to 1.06); RD 0% (95% CI –5.4% to 5.6%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Pulmonary function improvement:** No information **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No information
High dose steroids **High dose steroids may not improve dyspnea and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
COLDSTER trial *(32)*, Dhooria et al.; Peer reviewed; 2022	Patients with P-ACC (dyspnea and/or lung radiological abnormalities after 21 to 49 days of acute COVID-19). 65 assigned to prednisone 40 mg a day descending progressively to 10 mg a day for 6 weeks and 65 assigned to prednisone 10 mg a day for 6 weeks	Mean age 57, male 68%, one comorbidity 73%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** No information **Dyspnea improvement:** RR 1 (95% CI 0.87 to 1.15); RD 0% (95% CI –11.1% to 12.7%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Pulmonary function improvement:** No information **Radiological response:** Very low certainty ⊕◯◯◯ **Adverse events:** RR 0.92 (95% CI 0.75 to 1.13); RD –6.2% (95% CI –19.3% to 10%); Low certainty ⊕⊕◯◯ **Severe adverse events:** Very low certainty ⊕◯◯◯
Nebivolol **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**

RCT					
Dal Negro et al *(33)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 84 days of acute COVID-19). 8 assigned to Nebivolol 2.5 mg a day and 8 assigned to standard of care.	Mean age 50.5 ± 17.2, male 63%	NR	High risk of bias Notes: Concealment of allocation and blinding probably inappropriate.	**HRQL improvement:** No information **Dyspnea improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** No information **Pulmonary function improvement:** No information **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No
Respiratory training/rehabilitation **Respiratory training/rehabilitation probably improves HRQL and may improve dyspnea. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
ENO Breathe trial *(34)*, Philip et al.; Peer reviewed; 2022	Patients with P-ACC (dyspnea and/or lung radiological abnormalities after 30 days of acute COVID-19). 58 assigned to ENO Breathe 6-week program and 71 assigned to standard of care.	Mean age 49.5 ± 12, male 17.3%, interval between COVID-19 and enrolment 320 days, hospitalization during COVID-19 17.3%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** RR 1.73 (95% CI 1.28 to 2.34); RD 25.5% (95% CI 9.8% to 46.7%); Moderate certainty ⊕⊕⊕◯ **Dyspnea improvement:**

McNarry et al. *(35)*; Peer reviewed; 2022	Patients with P-ACC (dyspnea and/or lung radiological abnormalities after acute COVID-19). 37 assigned to inspiratory muscle training 3 sessions a week for 8 weeks and 37 assigned to standard of care.	Mean age 46.6 ± 12, male 12.8%, interval between COVID-19 and enrolment 270 days	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate. Intention-to-treat (ITT) analysis for primary outcome not available.	RR 1.88 (95% CI 1.43 to 2.47); RD 22.9% (95% CI 10.1% to 39.7%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Pulmonary function improvement:** Very low certainty ⊕◯◯◯ **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No
Srinivasan et al. *(36)*; Peer reviewed; 2022	Patients with P-ACC (dyspnea and/or lung radiological abnormalities after acute COVID-19). 24 assigned to respiratory training 3 times a day for 6 weeks and 24 assigned to standard of care.	NR	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Rodriguez-Blanco et al; *(27)* Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 40 days of acute COVID-19). 24 assigned to respiratory training (10 breathing and strength-based exercises) for 14 days, and 24 assigned to standard of care.	Mean age 40.7, male 22.91%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
InsCOVID trial *(37)*; Palau et al; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 90 days of acute COVID-19). 13 assigned to inspiratory muscle training twice a day for 12 weeks and 13 assigned to standard of care.	Mean age 50.4 ± 12.2, male 58%, hypertension 12%, interval between COVID-19 and enrolment 362 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	

RECOVER trial. *(38)*, Romanet et al.; Preprint; 2022	Patients with P-ACC (dyspnea and/or lung radiological abnormalities after 90 days of acute COVID-19). 27 assigned to endurance training rehabilitation (ETR) two (1 h) sessions per week for 10 weeks and 33 assigned to standard of care.	Mean age 58.2, male 61.6%, diabetes 36.7%, chronic lung disease 8.3%, chronic heart disease 5%, cancer 5%, interval between COVID-19 and enrolment 173 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Vallier et al; *(39)* Peer reviewed; 2022	Patients with P-ACC (dyspnea and/or lung radiological abnormalities after acute COVID-19). 8 assigned to home pulmonary rehabilitation four times a week for 4 weeks and 9 assigned to inpatient rehabilitation four times a week for 4 weeks	Mean age 54.8 ± 16, male 70.6%, interval between COVID-19 and enrolment 141 days, hospitalization during COVID-19 76.5%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** Very low certainty ⊕◯◯◯ **Dyspnea improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Pulmonary function improvement:** No information **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No information

Rutkowski et al *(40)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after of acute COVID-19). 18 assigned to VR respiratory training five sessions a week for 3 weeks and 14 assigned to conventional respiratory training.	Mean age 57.8 ± 4.9, male 37.5%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** No information **Dyspnea improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Pulmonary function improvement:** No information **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No information
Kusumawardani et al *(41)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after acute COVID-19). 10 assigned to incentive spirometry 5 times a day for four weeks and 10 assigned to conventional respiratory training.	Mean age 46, male 65%, hypertension 5%, diabetes 5%, obesity 55%, interval between COVID-19 and enrolment 22.5 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Dyspnea improvement:** No information **Functional capacity improvement:** No information **Pulmonary function improvement:** Very low certainty ⊕◯◯◯ **Radiological response:** No information **Adverse events:**

					No information **Severe adverse events:** No information
High dose steroids **High dose steroids may not improve dyspnea and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Bazdyrev et al. *(42)*; Peer reviewed; 2022	Patients with P-ACC (dyspnea and/or lung radiological abnormalities after acute COVID-19). 29 assigned to treamid 50 mg a day for 28 days and 30 assigned to standard of care.	Mean age 55 ± 11, male 44.1%	NR	Low risk of bias	**HRQL improvement:** No information **Dyspnea improvement:** RR 1.96 (95% CI 0.9 to 4.25); RD 21.7% (95% CI –2.3% to 73.7%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** RR 1.10 (95% CI 0.64 to 1.90); RD 4.3% (95% CI –16.2% to 39.8%); Low certainty ⊕⊕◯◯ **Pulmonary function improvement:** RR 2.48 (95% CI 1 to 6.17); RD 24.7% (95% CI 0% to 86.1%); Low certainty ⊕⊕◯◯ **Radiological**

					response: Very low certainty ⊕◯◯◯ **Adverse events:** RR 1.19 (95% CI 0.56 to 2.50); RD –5.5% (95% CI –12.7% to 43.6%); Low certainty ⊕⊕◯◯ **Severe adverse events:** No information

Table 4. Description of included studies and interventions effects for PCC neurocognitive symptoms

Actovegin **Actovegin may improve cognition. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Kutashov et al *(15)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after NR days of acute COVID-19). 222 assigned to Actovegin 1200 mg a day for 60 days and 222 assigned to standard of care.	Mean age 67.6, male 31.98%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cognitive improvement:** RR 1.19 (95% CI 1.06 to 1.33); RD 12.7% (95% CI 4.2% to 22.3%); Low certainty ⊕⊕◯◯ **Depression improvement:** No information

					Adverse events: No information **Severe adverse events:** No information
Hyperbaric oxygen (HBO) **HBO may improve HRQL. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Zilberman-Itskovich et al. *(43)*; Peer reviewed; 2022	Patients with P-ACC (neurocognitive symptoms after 90 days of acute COVID-19). 37 assigned to HBO 1 session a day for 40 days and 36 assigned to standard of care.	Mean age 48, male 39.7%, hypertension 8.2%, diabetes 2.7%, chronic lung disease 0%, asthma 4.1%, cancer 0%, obesity 27.4%, interval between COVID-19 and enrolment 165 days, hospitalization during COVID-19 16.4%	NR	Low risk of bias	**HRQL improvement:** RR 1.30 (95% CI 0.84 to 2); RD 13.9% (95% CI –7.4% to 46.9%); Low certainty ⊕⊕◯◯ **Overall symptom improvement:** No information **Cognitive improvement:** Very low certainty ⊕◯◯◯ **Depression improvement:** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Severe adverse events:** No information

Transcutaneous auricular vagus nerve stimulation (taVNS) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Badran et al. *(44)*; Preprint; 2022	Patients with P-ACC (neurocognitive symptoms after acute COVID-19). 6 assigned to transcutaneous auricular vagus nerve stimulation (taVNS) 2 (1 h) sessions a day for 4 weeks and 6 assigned to standard of care.	Mean age 48.5 ± 11.3, male 33.3%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cognitive improvement:** No information **Depression improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Transcranial direct current stimulation (tDCS) tDCS may not improve fatigue and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Oliver-Mas et al. *(29)*; Preprint; 2022	Patients with P-ACC (asthenia or fatigue after 180 days of acute COVID-19). 23 assigned to transcranial direct current stimulation	Mean age 45.6, male 21.3%, hypertension 12.8%, diabetes 4.3%, interval between COVID-19 and enrolment 620 days, hospitalization during COVID-19	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information

	(tDCS) 1 session a week for 8 weeks and 24 assigned to standard of care.	14.9%			**Cognitive improvement:** RR 0.59 (95% CI 0.33 to 1.05); RD –27.5% (95% CI –44.8% to 3.4%); Low certainty ⨁⨁◯◯ **Depression improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Table 5. Description of included studies and interventions effects for PCC olfactory and/or gustatory dysfunction

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
ADAPT-232 (adaptogens) **ADAPT-232 may not improve olfactory symptoms. However, certainty of the evidence was low. Further research is needed.**					
RCT					
Karosanidze et al. *(16)*; Peer reviewed; 2022	Patients with P-ACC (asthenia or fatigue after 30 days of acute COVID-19). 49 assigned to ADAPT-232 (adaptogens) 60 mL a day for 14 days and 50 assigned to standard of care.	Mean age 48.9, male 14%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** RR 0.89 (95% CI 0.79 to 1.01); RD –10.3% (95% CI –20.5% to 1.4%); Low certainty ⊕⊕◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Olfactory training **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and**

					GRADE certainty of the evidence
RCT					
Di Stadio et al. *(45)*; Peer reviewed; 2022	Patients with P-ACC (olfactory and/or gustatory dysfunction after 180 days of acute COVID-19). 76 assigned to olfactory training and 88 assigned to standard of care.	Mean age 40.7, male 27.6%, hypertension 1.7%, diabetes 0%, chronic heart disease 5.2%	Steroids 44%, vitamins 20.7%, alpha lipoic/nicetile 26.7%	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⊕◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Pires et al. *(46)*; Preprint; 2022	Patients with P-ACC (olfactory and/or gustatory dysfunction after 30 days of acute COVID-19). 26 assigned to advanced olfactory training with 8 essential oils: rose, eucalyptus, clove and lemon, citronella, mint, vanilla and cedarwood and 54 assigned to standard of care.	Mean age 37.6, male 35%	Steroids (nasal) 23.8%	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVANOS trial *(47)*, Lechner et al; Peer reviewed; 2022	Patients with P-ACC (olfactory and/or gustatory dysfunction after 30 days of acute COVID-19). 25 assigned to olfactory training for 12 weeks and 26 assigned to standard of care.	Mean age 44, male 13.8%, hypertension 8.9%, diabetes 1.1%, chronic lung disease 0%, asthma 12.6%, chronic heart disease 0%, cancer 2.1%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	

Palmitoylethanolamide + Luteolin

Palmitoylethanolamide + Luteolin may not improve olfactory symptoms. However, certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence

RCT					
Di Stadio et al. *(45)*; Peer reviewed; 2022	Patients with P-ACC (olfactory and/or gustatory dysfunction after 180 days of acute COVID-19). 88 assigned to palmitoylethanolamide + luteolin 700/70 mg a day and 38 assigned to standard of care.	Mean age 42.1, male 24.6%, hypertension 1.8%, diabetes 0%, chronic heart disease 3.6%	Steroids 32.5%, vitamins 15.8%, alpha lipoic/nicetile 14.9%	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** RR 1.11 (95% CI 0.68 to 1.81); RD 4.1% (95% CI –11.7% to 29.7%); Low certainty ⊕⊕◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Steroids (nasal)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
RC 4-7-2020 trial *(48)*, Abdelalim et al.; Peer reviewed; 2022	Patients with P-ACC (olfactory and/or gustatory dysfunction after acute COVID-19). 50 assigned to Mometasone 2 puffs (100 µg) once daily in each nostril for 3 weeks and 50 assigned to	Mean age 29, male 46%, hypertension 14%, diabetes 16%, hospitalization during COVID-19 31%	Steroids 13%	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:**

	standard of care.				Very low certainty ⊕◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Steroids **Steroids may not improve olfactory nor gustatory symptoms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Vaira et al. *(49)*; Peer reviewed; 2022	Patients with P-ACC (olfactory and/or gustatory dysfunction after acute COVID-19). 9 assigned to prednisone 1 mg/kg a day and 9 assigned to standard of care.	Mean age 42.1, male 38.8%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** RR 1.09 (95% CI 0.83 to 1.44); RD 3.3% (95% CI –6.2% to 16.1%); Low certainty ⊕⊕◯◯ **Gustatory symptoms improvement:** RR 1.01 (95% CI 0.67 to 1.53); RD 0.5% (95% CI –14.6% to 23.3%); Low certainty ⊕⊕◯◯
Schepens et al *(50)*; Peer reviewed; 2022	Patients with post COVID-19 condition (Olfactory and/or gustatory dysfunction after 28 days of acute COVID-19). 57 assigned to Prednisone 40 mg a day for 10 days and 56 assigned to standard of care.	Median age 49, male 36.5%, interval between COVID-19 and enrolment 56 days	Vaccinated 79.1%	Low risk of bias	

					Adverse events: No information **Severe adverse events:** No information
Theophylline (nasal) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
SCENT2 trial *(51)*; Gupta et al; Peer reviewed; 2022	Patients with post COVID-19 condition (Olfactory and/or gustatory dysfunction after 90 days of acute COVID-19). 26 assigned to Theophylline (nasal) 400 mg twice a day for 6 weeks and 25 assigned to standard of care.	Mean age 44.7, male 29.4%, interval between COVID-19 and enrolment 387 days	NR	Low risk of bias	**HRQL improvement:** Very low certainty ⨁◯◯◯ **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⨁◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** Very low certainty ⨁◯◯◯

Table 6. Description of included studies and interventions effects for PCC cardiovascular system symptoms

Ivabradine **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Jadhav et al. *(52)*; Peer reviewed; 2022	Patients with P-ACC (cardiovascular symptoms after 0 to 14 days of acute COVID-19). 25 assigned to Ivabradine 5 to 10 mg and 25 assigned to standard of care.	Mean age 48.8 ± 7.66	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Tachycardia improvement:** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Severe adverse events:** No information

Table 7. Description of included studies and interventions effects for PCC psychological distress

Virtual reality informational video Virtual reality informational video may improve depression, post-traumatic stress, and psychological distress. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
ICU-VR trial *(53)*, Vlake et al.; Peer reviewed; 2022	Patients with P-ACC (psychological distress after 90 days of acute COVID-19). 45 assigned to virtual reality 14-minute informational video session once and 44 assigned to standard of care.	Mean age 60, male 36%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Depression improvement:** RR 1.21 (95% CI 0.95 to 1.54); RD 14% (95% CI –3.7% to 36.7%); Low certainty ⊕⊕◯◯ **Post-traumatic stress improvement:** RR 1.18 (95% CI 0.98 to 1.42); RD 13.8% (95% CI –1.5% to 32.3%); Low certainty ⊕⊕◯◯ **Psychological distress improvement:** RR 1.49 (95% CI 1.08 to 2.05); RD 25.5% (95% CI 4.1% to 55.1%); Low certainty ⊕⊕◯◯ **Adverse events:** No information **Severe adverse events:** No information

Table 8. Description of included studies and interventions effects for P-ACC-related thromboembolic risk

Anticoagulants (prophylactic dose) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
MICHELLE trial *(54)*, Ramacciotti et al.; Peer reviewed; 2022	Patients with P-ACC (at increased risk of VTE after acute COVID-19). 159 assigned to rivaroxaban 10 mg a day for 35 days and 159 assigned to standard of care.	Mean age 57.1, male 60%, interval between COVID-19 and enrolment 8 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias to symptoms, VTE and adverse events outcomes.	**Mortality:** Very low certainty ⨁◯◯◯ **HRQL improvement:** No information **VTE (symptomatic):** Very low certainty ⨁◯◯◯ **Major bleeding:** No information **Severe adverse events:** No information

Table 9. Description of included studies and interventions effects for PIMS-TS

Steroids Steroids may reduce time to discharge and respiratory support requirements. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Swissped RECOVERY trial *(55)*; Welzel et al; Peer reviewed; 2022	Patients with PIMS-TS. 37 assigned to methylprednisolone 10 mg/kg a day for 3 days and 38 assigned to IVIG 2 gr/kg once	Mean age 9.1, male 75%, underlying chronic disease 11%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**Mortality:** No information **Time to discharge reduction:** RR 1.09 (95% CI 0.88 to 1.39); RD 4.5% (95% CI -6% to 19.5%); Low certainty ⨁⨁◯◯ **Respiratory support:** RR 0.49 (95% CI 0.27 to 0.89); RD -28.2% (95% CI -40.5% to -5.9%); Low certainty ⨁⨁◯◯ **Inotropic requirements:** Very low certainty ⨁◯◯◯ **LVEF <55%:** Very low certainty ⨁◯◯◯ **Arrhythmia:** Very low certainty ⨁◯◯◯ **VTE:** Very low certainty ⨁◯◯◯ **Major bleeding:** No information

Table 10. Description of included studies and interventions effects for P-ACC prophylaxis

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
Convalescent plasma **Convalescent may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.**					
RCT					
CSSC-004 trial *(56)*; Kelly et al; Preprint; 2022	Patients with mild to moderate COVID-19. 445 assigned to convalescent plasma 250 ml once and 437 assigned to standard of care.	Median age 43, male 42.6%, hypertension 23.5%, diabetes 8.2%, obesity 16%,	Vaccinated 22%	High risk of bias Notes: Significant loss to follow-up	**Mortality:** No information **HRQL improvement:** No information **P-ACC:** RR 0.93 (95% CI 0.77 to 1.12); RD -2.4% (95% CI -7.9% to 4.2%); Low certainty ⨁⨁◯◯ **Adverse events:** No information **Severe adverse events:** No information
Fluvoxamine **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
COVID-OUT - Ivermectin trial *(57)*; Bramante et al; Preprint; 2022	Patients with mild to moderate COVID-19. 298 assigned to Fluvoxamine 50 mg once followed by 100 mg a day for 14 days and 297 assigned to	Median age 44.5, male 45.8%, hypertension 26.9%, diabetes 1.1%, obesity 47.2%,	Corticosteroids 1.5%, monoclonal antibodies 4.2%; Vaccinated 56.4%	High risk of bias Notes: Significant loss to follow-up	**Mortality:** No information **HRQL improvement:** No information **P-ACC:** RR 1.36 (95% CI 0.8 to

	standard of care.				2.3); RD 2.7% (95% CI -1.5% to 9.6%); Very low certainty ⨁◯◯◯ **Adverse events:** No information **Severe adverse events:** No information
Ivermectin **Ivermectin may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
COVID-OUT - Ivermectin trial *(57)*; Bramante et al; Preprint; 2022	Patients with mild to moderate COVID-19. 377 assigned to Ivermectin 390-470 mcg/kg per day for 3 days and 361 assigned to standard of care.	Median age 45.5, male 44%, hypertension 26.7%, diabetes 2%, obesity 48.8%	Corticosteroids 1.5%, monoclonal antibodies 4.2%; Vaccinated 52.2%	High risk of bias Notes: Significant loss to follow-up	**Mortality:** No information **HRQL improvement:** No information **P-ACC:** RR 0.99 (95% CI 0.61 to 1.62); RD 0% (95% CI -1.7% to -2.6%); Low certainty ⨁⨁◯◯ **Adverse events:** No information **Severe adverse events:** No information
Metformin **Metformin may reduce P-ACC. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**

RCT					
COVID-OUT - Metformin trial *(57)*; Bramante et al; Preprint; 2022	Patients with mild to moderate COVID-19. 564 assigned to metformin 1500 mg a day for 14 days and 561 assigned to standard of care.	Median age 45.5, male 45.3%, hypertension 22.8%, diabetes 1.6%, obesity 47.4%	Steroids 1.5%, remdesivir %, monoclonal antibodies 4.2%; Vaccinated 55.6%	High risk of bias Notes: Significant loss to follow-up	**Mortality:** No information **HRQL improvement:** No information **P-ACC:** RR 0.59 (95% CI 0.39 to 0.88); RD -4.3% (95% CI -6.4% to -1.2%); Low certainty ⊕⊕◯◯ **Adverse events:** No information **Severe adverse events:** No information
Remdesivir **Remdesivir may not reduce P-ACC. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
SOLIDARITY - Finland trial *(58)*; Nevalainen et al; Peer reviewed; 2022	Patients with post COVID-19 condition (P-ACC prophylaxis after 0 days of acute COVID-19). 98 assigned to Remdesivir 200 mg once followed by 100 mg a day for 10 days and 83 assigned to standard of care.	Mean age 58.4, male 60.2%, diabetes 22.1%, hospitalization during COVID-19 100%	Corticosteroids 71.8%	Low risk of bias	**Mortality:** Very low certainty ⊕◯◯◯ **HRQL improvement:** No information **P-ACC:** RR 1.06 (95% CI 0.53 to 2.13); RD 0.8% (95% CI -6.9% to 16.4%); Low certainty ⊕⊕◯◯ **Adverse events:** No information **Severe adverse events:** No

					information

References

1. A clinical case definition of post COVID-19 condition by a Delphi consensus. 6 October, 2021. Available from: https://apps.who.int/iris/rest/bitstreams/1376291/retrieve
2. A clinical case definition for post COVID-19 condition in children and adolescents by expert consensus (16 February 2023). Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post-COVID-19-condition-CA-Clinical-case-definition-2023-1
3. Zhang H, Zang C, Xu Z, Zhang Y, Xu J, Bian J, et al. Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes. Nat Med [Internet]. 2022 Dec 1 [cited 2023 Jan 6]; Available from: https://www.nature.com/articles/s41591-022-02116-3
4. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021 Apr;27(4):601–15.
5. Malik P, Patel K, Pinto C, Jaiswal R, Tirupathi R, Pillai S, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)—A systematic review and meta-analysis. Journal of Medical Virology. 2022 Jan;94(1):253–62.
6. Han Q, Zheng B, Daines L, Sheikh A. Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of One-Year Follow-Up Studies on Post-COVID Symptoms. Pathogens. 2022 Feb 19;11(2):269.
7. World Health Organization. Clinical management of COVID-19 - Living guideline. Geneva: WHO; 15 September 2022. Available from: https://reliefweb.int/report/world/clinical-management-covid-19-living-guideline-15-september-2022
8. The L·OVE Platform. Methods for the special L·OVE of coronavirus infection [Internet] Santiago: Epistemonikos Foundation; 2020 [cited 7 December 2020]. Available from: https://app.iloveevidence.com/covid-19
9. Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al. GRADE guidelines: 13. Preparing Summary of Findings tables and evidence profiles—continuous outcomes. Journal of Clinical Epidemiology. 2013 Feb;66(2):173–83.
10. Hultcrantz M, Rind D, Akl EA, et al. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol 2017; 87: 4–13.
11. Zeng L, Brignardello-Petersen R, Hultcrantz M, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. Journal of Clinical Epidemiology 2021; 137: 163–75.

12. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. Available from: https://doi.org/10.1136/bmj.l4898.
13. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336: 924–26.
14. Chudzik M, Burzyńska M, Kapusta J. Use of 1-MNA to Improve Exercise Tolerance and Fatigue in Patients after COVID-19. Nutrients. 2022 Jul 22;14(15):3004.
15. Kutashov VA. Actovegin use in patients with cognitive impairment after coronavirus infection (COVID-19). RJTAO. 2021 Apr 25;13(2):65–72.
16. Karosanidze I, Kiladze U, Kirtadze N, Giorgadze M, Amashukeli N, Parulava N, et al. Efficacy of Adaptogens in Patients with Long COVID-19: A Randomized, Quadruple-Blind, Placebo-Controlled Trial. Pharmaceuticals. 2022 Mar 11;15(3):345.
17. Tosato M, Calvani R, Picca A, Ciciarello F, Galluzzo V, Coelho-Júnior HJ, et al. Effects of l-Arginine Plus Vitamin C Supplementation on Physical Performance, Endothelial Function, and Persistent Fatigue in Adults with Long COVID: A Single-Blind Randomized Controlled Trial. Nutrients. 2022 Nov 23;14(23):4984.
18. Hawkins J, Hires C, Keenan L, Dunne E. 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. Complementary Therapies in Medicine. 2022 Aug;67:102823.
19. Hansen KS, Mogensen TH, Agergaard J, Schiøttz-Christensen B, Østergaard L, Vibholm LK, et al. High-dose coenzyme Q10 therapy versus placebo in patients with post COVID-19 condition: A randomized, phase 2, crossover trial. The Lancet Regional Health - Europe. 2022 Nov;100539.
20. Putilina MV, Teplova NV, Bairova KI, Petrikeeva AE, Shabalina NI. The result of prospective randomized study CITADEL — the efficacy and safety of drug cytoflavin in postcovid rehabilitation. Z nevrol psikhiatr im SS Korsakova. 2021;121(10):45.
21. Rathi A, Jadhav SB, Shah N. A Randomized Controlled Trial of the Efficacy of Systemic Enzymes and Probiotics in the Resolution of Post-COVID Fatigue. Medicines. 2021 Aug 30;8(9):47.
22. Kharaeva Z, Shokarova A, Shomakhova Z, Ibragimova G, Trakhtman P, Trakhtman I, 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):2203.

23. Botek M, Krejčí J, Valenta M, McKune A, Sládečková B, Konečný P, et al. Molecular Hydrogen Positively Affects Physical and Respiratory Function in Acute Post-COVID-19 Patients: A New Perspective in Rehabilitation. IJERPH. 2022 Feb 10;19(4):1992.
24. Deshpande S, Mundhe N, Deshpande V, Tamoli S, Mahadik S, Pawar V. Potential use of Immunodaat® (Botanical extract of Elderberry -Sambucus Nigra L.) in the management of Post Covid-19 symptoms- a comparative, multi-centric, randomized, clinical study [Internet]. Allergy and Immunology; 2022 Oct [cited 2023 Mar 23]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.10.04.22280680
25. Gaylis NB, Ritter A, Kelly SA, Pourhassan NZ, Tiwary M, Sacha JB, et al. Reduced Cell Surface Levels of C-C Chemokine Receptor 5 and Immunosuppression in Long Coronavirus Disease 2019 Syndrome. Clinical Infectious Diseases. 2022 Sep 30;75(7):1232–4.
26. Nambi G, Abdelbasset WK, Alrawaili SM, Elsayed SH, Verma A, Vellaiyan A, et al. Comparative effectiveness study of low versus high-intensity aerobic training with resistance training in community-dwelling older men with post-COVID 19 sarcopenia: A randomized controlled trial. Clin Rehabil. 2022 Jan;36(1):59–68.
27. Rodriguez-Blanco C, Bernal-Utrera C, Anarte-Lazo E, Gonzalez-Gerez JJ, Saavedra-Hernandez M. A 14-Day Therapeutic Exercise Telerehabilitation Protocol of Physiotherapy Is Effective in Non-Hospitalized Post-COVID-19 Conditions: A Randomized Controlled Trial. JCM. 2023 Jan 18;12(3):776.
28. Thomas R, Williams M, Aldous J, Yanagisawa Y, Kumar R, Forsyth R, et al. A Randomised, Double-Blind, Placebo-Controlled Trial Evaluating Concentrated Phytochemical-Rich Nutritional Capsule in Addition to a Probiotic Capsule on Clinical Outcomes among Individuals with COVID-19—The UK Phyto-V Study. COVID. 2022 Mar 22;2(4):433–49.
29. Oliver-Mas S, Delgado-Alonso C, Delgado-Álvarez A, Díez-Cirarda M, Cuevas C, Fernández-Romero L, et al. Transcranial Direct Current Stimulation (tDCS) for Post-COVID Fatigue: A Randomized, Double-Blind, Controlled Pilot Study. SSRN Journal [Internet]. 2022 [cited 2022 Dec 21]; Available from: https://www.ssrn.com/abstract=4216601
30. Santana K, França E, Sato J, Silva A, Queiroz M, de Farias J, et al. Non-invasive brain stimulation for fatigue in post-acute sequelae of SARS-CoV-2 (PASC). Brain Stimulation. 2023 Jan;16(1):100–7.
31. King M, Byrne A, Denehy L, Graham P, Douglas B, de Toni P, et al. Feasibility of a Group-Based Telerehabilitation Intervention for Long COVID Management. [Internet].

In Review; 2022 Mar [cited 2022 Dec 27]. Available from: https://www.researchsquare.com/article/rs-1452186/v1

32. Dhooria S, Chaudhary S, Sehgal IS, Agarwal R, Arora S, Garg M, et al. High-dose versus low-dose prednisolone in symptomatic patients with post-COVID-19 diffuse parenchymal lung abnormalities: an open-label, randomised trial (the COLDSTER trial). Eur Respir J. 2022 Feb;59(2):2102930.
33. Dal Negro RW, Turco P, Povero M. Nebivolol: an effective option against long-lasting dyspnoea following COVID-19 pneumonia - a pivotal double-blind, cross-over controlled study. Multidis Res Med [Internet]. 2022 Dec 23 [cited 2023 Mar 23];17. Available from: https://mrmjournal.org/mrm/article/view/886
34. Philip KEJ, Owles H, McVey S, Pagnuco T, Bruce K, Brunjes H, et al. An online breathing and wellbeing programme (ENO Breathe) for people with persistent symptoms following COVID-19: a parallel-group, single-blind, randomised controlled trial. The Lancet Respiratory Medicine. 2022 Sep;10(9):851–62.
35. McNarry MA, Berg RMG, Shelley J, Hudson J, Saynor ZL, Duckers J, et al. Inspiratory muscle training enhances recovery post-COVID-19: a randomised controlled trial. Eur Respir J. 2022 Oct;60(4):2103101.
36. Srinivasan V., Kandakurti P.K., Alagesan J., Suganthirababu P., Jenifer Augustina S., Anitha A., et al. Efficacy of pursed lip breathing with bhastrika pranayama vs incentive spirometry in rehabilitating post Covid 19 follow up-a randomized control study. Turkish Journal of Physiotherapy and Rehabilitation. 2021;32(3):402–7.
37. Palau P, Domínguez E, Gonzalez C, Bondía E, Albiach C, Sastre C, et al. Effect of a home-based inspiratory muscle training programme on functional capacity in postdischarged patients with long COVID: the InsCOVID trial. BMJ Open Resp Res. 2022 Dec;9(1):e001439.
38. Romanet C, Wormser J, Fels A, Lucas P, Prudat C, Sacco E, et al. Effectiveness of endurance training rehabilitation after hospitalisation in intensive care for COVID-19-related acute respiratory distress syndrome on dyspnoea (RECOVER): a randomised controlled, open-label multicentre trial [Internet]. Respiratory Medicine; 2022 Aug [cited 2022 Dec 30]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.08.29.22279327
39. Vallier JM, Simon C, Bronstein A, Dumont M, Jobic A, Paleiron N, et al. Randomized controlled trial of home-based vs. hospital-based pulmonary rehabilitation in post COVID-19 patients. Eur J Phys Rehabil Med [Internet]. 2023 Jan [cited 2023 Feb 9];

Available from: https://www.minervamedica.it/index2.php?show=R33Y9999N00A23012602
40. Rutkowski S, Bogacz K, Rutkowska A, Szczegielniak J, Casaburi R. Inpatient post-COVID-19 rehabilitation program featuring virtual reality—Preliminary results of randomized controlled trial. Front Public Health. 2023 Feb 6;11:1121554.
41. Kusumawardani RI, Tinduh D, Poerwandari D, Marhana IA, Melaniani S. The effectiveness of incentive spirometry exercise on pulmonary function in COVID-19 survivors: a randomized controlled trial study. Bali Medical Journal. 2023;12(1):539–44.
42. Bazdyrev E, Panova M, Brachs M, Smolyarchuk E, Tsygankova D, Gofman L, et al. Efficacy and safety of Treamid in the rehabilitation of patients after COVID-19 pneumonia: a phase 2, randomized, double-blind, placebo-controlled trial [Internet]. In Review; 2022 Jul [cited 2022 Dec 27]. Available from: https://www.researchsquare.com/article/rs-1845321/v1
43. Zilberman-Itskovich S, Catalogna M, Sasson E, Elman-Shina K, Hadanny A, Lang E, et al. Hyperbaric oxygen therapy improves neurocognitive functions and symptoms of post-COVID condition: randomized controlled trial. Sci Rep. 2022 Jul 12;12(1):11252.
44. Badran BW, Huffman SM, Dancy M, Austelle CW, Bikson M, Kautz SA, et al. A pilot randomized controlled trial of supervised, at-home, self-administered transcutaneous auricular vagus nerve stimulation (taVNS) to manage long COVID symptoms [Internet]. In Review; 2022 Jun [cited 2022 Dec 30]. Available from: https://www.researchsquare.com/article/rs-1716096/v1
45. Di Stadio A, Gallina S, Cocuzza S, De Luca P, Ingrassia A, Oliva S, et al. Treatment of Persistent COVID-19 Smell Dysfunction with Olfactory Training, Co-Ultramicronized Palmitoylethanolamide with Luteolin, or Combined Therapy: Results of Double-Blinded Multicenter Clinical Trial. SSRN Journal [Internet]. 2022 [cited 2022 Dec 21]; Available from: https://www.ssrn.com/abstract=4261830
46. Pires ÍAT, Steffens ST, Mocelin AG, Shibukawa DE, Leahy L, Saito FL, et al. Intensive Olfactory Training in Post-COVID Patients: A Randomized Multicenter Clinical Trial [Internet]. 2022 Jan [cited 2022 Dec 29]. Available from: https://preprints.scielo.org/index.php/scielo/preprint/view/3301/version/3492
47. Lechner M, Liu J, Counsell N, Gillespie D, Chandrasekharan D, Ta NH, et al. The COVANOS trial – insight into post-COVID olfactory dysfunction and the role of smell training. Rhin. 2022 Jun 1;60(3):188–99.

48. Abdelalim AA, Mohamady AA, Elsayed RA, Elawady MA, Ghallab AF. Corticosteroid nasal spray for recovery of smell sensation in COVID-19 patients: A randomized controlled trial. American Journal of Otolaryngology. 2021 Mar;42(2):102884.
49. Vaira LA, Hopkins C, Petrocelli M, Lechien JR, Cutrupi S, Salzano G, et al. Efficacy of corticosteroid therapy in the treatment of long- lasting olfactory disorders in COVID-19 patients. Rhin. 2020 Dec 1;0(0):0–0.
50. Schepens EJA, Blijleven EE, Boek WM, Boesveldt S, Stokroos RJ, Stegeman I, et al. Prednisolone does not improve olfactory function after COVID-19: a randomized, double-blind, placebo-controlled trial. BMC Med. 2022 Nov 16;20(1):445.
51. Gupta S, Lee JJ, Perrin A, Khan A, Smith HJ, Farrell N, et al. Efficacy and Safety of Saline Nasal Irrigation Plus Theophylline for Treatment of COVID-19–Related Olfactory Dysfunction: The SCENT2 Phase 2 Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg. 2022 Sep 1;148(9):830.
52. Kartik Pandurang J, Pankaj V J. Ivabradine versus carvedilol in the management of palpitation with sinus tachycardia among recovered COVID-19 patients. J Cardiol Cardiovasc Me. 2020 Dec 23;5(3):176–80.
53. Vlake JH, van Bommel J, Wils EJ, Bienvenu J, Hellemons ME, Korevaar TI, et al. Intensive Care Unit–Specific Virtual Reality for Critically Ill Patients With COVID-19: Multicenter Randomized Controlled Trial. J Med Internet Res. 2022 Jan 31;24(1):e32368.
54. Ramacciotti E, Barile Agati L, Calderaro D, Aguiar VCR, Spyropoulos AC, de Oliveira CCC, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. The Lancet. 2022 Jan;399(10319):50–9.
55. Welzel T, Atkinson A, Schöbi N, Andre MC, Bailey DGN, Blanchard-Rohner G, et al. Methylprednisolone versus intravenous immunoglobulins in children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS): an open-label, multicentre, randomised trial. The Lancet Child & Adolescent Health. 2023 Feb;S2352464223000202.
56. Gebo KA, Heath SL, Fukuta Y, Zhu X, Baksh S, Abraham AG, et al. Early Treatment, Inflammation and Post-COVID Conditions [Internet]. Infectious Diseases (except HIV/AIDS); 2023 Feb [cited 2023 Mar 17]. Available from: http://medrxiv.org/lookup/doi/10.1101/2023.02.13.23285855
57. Bramante C, Buse JB, Liebovitz D, Nicklas J, Puskarich M, Cohen KR, et al. Outpatient Treatment of COVID-19 and the Development of Long COVID Over 10 Months: A

Multi-Center, Quadruple-Blind, Parallel Group Randomized Phase 3 Trial [Internet]. SSRN; 2023 [cited 2023 Mar 14]. Available from: https://www.ssrn.com/abstract=4375620

58. Nevalainen OPO, Horstia S, Laakkonen S, Rutanen J, Mustonen JMJ, Kalliala IEJ, et al. Effect of remdesivir post hospitalization for COVID-19 infection from the randomized SOLIDARITY Finland trial. Nat Commun. 2022 Oct 18;13(1):6152.

Annex 1. Summary of findings tables

Summary of findings Table A1.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Actovegin
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Actovegin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Fatigue improvement	Relative risk: 1.54 (CI 95% 1.59 - 2.14) Based on data from 444 participants in 1 study Follow up 90 days	**471** per 1000	**725** per 1000 Difference: **254 more per 1000** (CI 95% 278 more - 537 more)	**Low** Due to very serious risk of bias[1]	Actovegin may improve fatigue

1. **Risk of Bias: very serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: no serious.** 95% CI include important benefits and harms;

Summary of findings Table A2.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: ADAPT-232
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	ADAPT-232	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Fatigue improvement	Relative risk 1.02 (95% CI 0.84 to 1.24) Based on data from 99 participants in 1 study Follow-up 21 days	**800** per 1000	**816** per 1000 Difference: **16 more per 1000** (95% CI 128 fewer to 192 more)	**Low** Due to very serious imprecision[a]	Adapt-232 may have little or no difference on fatigue improvement

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A3.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Cytoflavin

Comparator: Standard of care (SOC)

Outcome Timeframe	Study results and measurements	Absolute effect estimates SOC	 Cytoflavin	Certainty of the evidence (Quality of evidence)	Plain language summary
Fatigue improvement[a]	Relative risk 1.02 (95% CI 0.98 to 1.06) Based on data from 200 participants in 1 study Follow-up 25 days	**979** per 1000	**999** per 1000 Difference: **20 more per 1000** (95% CI 20 fewer to 21 more)	**Low** Due to serious risk of bias, Due to serious imprecision[b]	Cytoflavin may have little or no difference on fatigue improvement

a. Decrease in 12 units of the MFI score.
b. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.

Summary of findings Table A4.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Enzymes + probiotics
Comparator: Standard of care (SOC)

Outcome Timeframe	Study results and measurements	Absolute effect estimates SOC	 Enzymes + probiotics	Certainty of the evidence (Quality of evidence)	Plain language summary
Fatigue improvement	Relative risk 6.07 (95% CI 3.71 to 9.71) Based on data from 200 participants in 1 study Follow-up 25 days	**150** per 1000	**911** per 1000 Difference: **761 more per 1000** (95% CI 407 more to 850 more)	**Low** Due to serious risk of bias, Due to serious imprecision[a]	Enzymes + probiotics may increase fatigue improvement

a. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.

Summary of findings Table A5.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Phytochemicals
Comparator: Standard of care (SOC)

Outcome		Absolute effect estimates		

Timeframe	**Study results and measurements**	SOC	Phytochemicals	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
HRQL improvement	Relative risk: 1.33 (CI 95% 1.03 - 1.71) Based on data from 147 participants in 1 study Follow up 30 days	**543** per 1000	**722** per 1000 Difference: **179 more per 1000** (CI 95% 16 more - 386 more)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Phytochemicals may increase HRQL improvement
Fatigue improvement	Relative risk: 1.24 (CI 95% 0.95 - 1.62) Based on data from 147 participants in 1 study Follow up 30 days	**539** per 1000	**668** per 1000 Difference: **129 more per 1000** (CI 95% 27 fewer - 334 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Phytochemicals may increase fatigue improvement

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients;
2. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients;

Summary of findings Table A6.

Population: Patients with P-ACC-related asthenia or fatigue
Intervention: Transcranial direct current stimulation (tDCS)
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Transcranial direct current stimulation (tDCS)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Fatigue improvement	Relative risk: 1.36 (CI 95% 0.76 - 2.45) Based on data from 117 participants in 2 studies Follow up 32.5 days	**468** per 1000	**636** per 1000 Difference: **168 more per 1000** (CI 95% 112 fewer - 672 more)	**Low** Due to very serious imprecision[1]	Transcranial direct current stimulation (tdcs) may have little or no difference on fatigue improvement
HRQL improvement	Relative risk: 1.37 (CI 95% 1.09 - 1.71) Based on data from 70 participants in 1 study Follow up 35 days	**705** per 1000	**966** per 1000 Difference: **261 more per 1000** (CI 95% 63 more - 295 more)	**Low** Due to very serious imprecision[2]	Transcranial direct current stimulation (tdcs) may improve HRQL
Fatigue improvement	Relative risk: 0.95 (CI 95% 0.5 - 1.79) Based on data from 47 participants in 1 study Follow up 25 days	**458** per 1000	**435** per 1000 Difference: **23 fewer per 1000** (CI 95% 229 fewer - 362 more)	**Low** Due to very serious imprecision[3]	Transcranial direct current stimulation (tdcs) may have little or no difference on fatigue improvement

1. **Imprecision: very serious.** 95% CI include important benefits and harms;
2. **Imprecision: very serious.** 95% CI include important benefits and harms;
3. **Imprecision: very serious.** 95% CI include important benefits and harms;

Summary of findings Table A7.

Population: Patients with P-ACC-related dyspnea
Intervention: ADAPT-232
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	ADAPT-232		
Dyspnea improvement	Relative risk 1.0 (95% CI 0.94 to 1.06) Based on data from 99 participants in 1 study Follow-up 21 days	**980** per 1000	**980** per 1000	**Low** Due to very serious imprecision[a]	ADAPT-232 may have little or no difference on dyspnea improvement
		Difference: **0 fewer per 1000** (95% CI 59 fewer to 20 more)			

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A8.

Population: Patients with P-ACC-related dyspnea
Intervention: Endurance training
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Endurance training	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
HRQL improvement[a]	Relative risk 1.48 (95% CI 0.92 to 2.37) Based on data from 60 participants in 1 study Follow-up 21 days	**441** per 1000	**980** per 1000 Difference: **0 fewer per 1000** (95% CI 59 fewer to 20 more)	**Low** Due to serious risk of bias, Due to serious imprecision[b]	Endurance training may increase HRQL improvement
Dyspnea improvement[c]	Relative risk 2.03 (95% CI 0.98 to 4.21) Based on data from 60 participants in 1 study Follow-up 21 days	**236** per 1000	**980** per 1000 Difference: **0 fewer per 1000** (95% CI 59 fewer to 20 more)	**Low** Due to serious risk of bias, Due to serious imprecision[d]	Endurance training may increase dyspnea improvement

a. Increment of 7 units in the SF-12 scale.
b. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.
c. Increment of 7 units in the SF-12 scale.
d. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.

Summary of findings Table A9.

Population: Patients with P-ACC-related dyspnea
Intervention: High dose steroids (i.e., prednisone 40 mg a day)
Comparator: Standard dose steroids (i.e., prednisone 10 mg a day)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard dose steroids	**Absolute effect estimates** High dose steroids	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Dyspnea improvement	Relative risk 1.0 (95% CI 0.87 to 1.15) Based on data from 130 participants in 1 study Follow-up 42 days	**862** per 1000	**862** per 1000 Difference: **0 fewer per 1000** (95% CI 112 fewer to 129 more)	**Low** Due to serious risk of bias, Due to serious imprecision[a]	High dose steroids may have little or no difference on dyspnea improvement
Radiological response	Relative risk 1.33 (95% CI 0.69 to 2.59) Based on data from 60 participants in 1 study Follow-up 21 days	**185** per 1000	**246** per 1000 Difference: **61 more per 1000** (95% CI 57 fewer to 294 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[b]	We are uncertain whether high dose steroids increases or decreases radiological response
Adverse events	Relative risk 0.92 (95% CI 0.75 to 1.13) Based on data from 60 participants in 1 study Follow-up 21 days	**769** per 1000	**707** per 1000 Difference: **62 fewer per 1000** (95% CI 192 fewer to 100 more)	**Low** Due to serious risk of bias, Due to serious imprecision[c]	High dose steroids may have little or no difference on adverse events
Severe adverse events	Relative risk 3.0 (95% CI 0.32 to 28.09) Based on data from 60 participants in 1 study Follow-up 21 days	**15** per 1000	**45** per 1000 Difference: **30 more per 1000** (95% CI 10 fewer to 406 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[d]	We are uncertain whether high dose steroids increases or decreases severe adverse events

a. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.
b. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** 95% CI includes important benefits and harms.
c. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.
d. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A10.

Population: Patients with P-ACC-related dyspnea
Intervention: Respiratory training/rehabilitation
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	**Absolute effect estimates** Respiratory training	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
HRQL improvement	Relative risk: 1.73 (CI 95% 1.28 - 2.34) Based on data from 263 participants in 3 studies Follow up 109 days	**349** per 1000	**604** per 1000 Difference: **255 more per 1000** (CI 95% 98 more - 468 more)	**Moderate** Due to serious risk of bias[1]	Respiratory training/rehabilitation probably increases HRQL improvement
Dyspnea improvement	Relative risk: 1.88 (CI 95% 1.43 - 2.47) Based on data from 331 participants in 4 studies Follow up 85 days	**251** per 1000	**472** per 1000 Difference: **221 more per 1000** (CI 95% 108 more - 369 more)	**Low** Due to serious risk of bias, Due to serious inconsistency[2]	Respiratory training/rehabilitation may increase dyspnea improvement
Pulmonary function improvement	Relative risk: 1.39 (CI 95% 0.8 - 2.41) Based on data from 74 participants in 2 studies Follow up 66 days	**459** per 1000	**638** per 1000 Difference: **179 more per 1000** (CI 95% 92 fewer - 647 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether respiratory training/rehabilitation increases or decreases pulmonary function improvement

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias;
2. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.;
3. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** 95% CI include important benefits and harms;

Summary of findings Table A11.

Population: Patients with P-ACC-related dyspnea
Intervention: Treamid
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Treamid	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Functional capacity improvement	Relative risk 1.1 (95% CI 0.64 to 1.9) Based on data from 59 participants in 1 study Follow-up 28 days	**445** per 1000	**490** per 1000 Difference: **45 more per 1000** (95% CI 160 fewer to 401 more)	**Low** Due to very serious imprecision[a]	Treamid may have little or no difference on functional capacity improvement
Dyspnea improvement	Relative risk 1.96 (95% CI 0.9 to 4.25) Based on data from 59 participants in 1 study Follow-up 28 days	**227** per 1000	**445** per 1000 Difference: **218 more per 1000** (95% CI 23 fewer to 738 more)	**Low** Due to very serious imprecision[b]	Treamid may increase dyspnea improvement
Pulmonary function improvement	Relative risk 2.48 (95% CI 1.0 to 6.17) Based on data from 59 participants in 1 study Follow-up 28 days	**167** per 1000	**414** per 1000 Difference: **247 more per 1000** (95% CI 0 fewer to 863 more)	**Low** Due to very serious imprecision[c]	Treamid may increase pulmonary function improvement
Adverse events	Relative risk 1.19 (95% CI 0.56 to 2.5) Based on data from 59 participants in 1 study Follow-up 28 days	**290** per 1000	**345** per 1000 Difference: **55 more per 1000** (95% CI 128 fewer to 435 more)	**Low** Due to very serious imprecision[d]	Treamid may increase adverse events

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.
b. **Imprecision: very serious.** 95% CI includes important benefits and harms.
c. **Imprecision: very serious.** 95% CI includes important benefits and harms.
d. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A12.

Population: Patients with P-ACC-related neurocognitive symptoms
Intervention: Actovegin
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Actovegin		
Cognitive improvement	Odds ratio: 1.19 (CI 95% 1.06 - 1.33) Based on data from 444 participants in 1 study	**673** per 1000	**710** per 1000	**Low** Due to very serious risk of bias[1]	Actovegin may improve cognition
		Difference: **37 more per 1000** (CI 95% 13 more - 384 fewer)			

3. **Risk of Bias: very serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Indirectness: serious.** Non appropriately established MID; **Imprecision: no serious.** 95% CI include important benefits and harms;

Summary of findings Table A13.

Population: Patients with P-ACC-related neurocognitive symptoms
Intervention: Hyperbaric oxygen (HBO)
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	HBO	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
HRQL improvement	Relative risk 1.3 (95% CI 0.84 to 2.0) Based on data from 73 participants in 1 study	**469** per 1000	**610** per 1000 Difference: **141 more per 1000** (95% CI 75 fewer to 469 more)	**Low** Due to very serious imprecision[a]	HBO may increase HRQF improvement
Cognitive improvement	Odds ratio 2.84 (95% CI 1.09 to 7.37) Based on data from 73 participants in 1 study	**667** per 1000	**850** per 1000 Difference: **183 more per 1000** (95% CI 19 more to 22 more)	**Very low** Due to extremely serious imprecision, Due to serious indirectness[b]	We are uncertain whether HBO increases or decreases cognitive improvement
Depression improvement	Odds ratio 35.9 (95% CI 2.72 to 474.6) Based on data from 73 participants in 1 study Follow-up 28 days	**681** per 1000	**987** per 1000 Difference: **306 more per 1000** (95% CI 172 more to 312 more)	**Very low** Due to extremely serious imprecision, Due to serious indirectness[c]	We are uncertain whether HBO increases or decreases depression improvement

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.
b. **Indirectness: serious.** Non appropriately established minimal important difference (MID). **Imprecision: extremely serious.** 95% CI includes important benefits and harms.
c. **Indirectness: serious.** Non appropriately established MID. **Imprecision: extremely serious.** 95% CI includes important benefits and harms.

Summary of findings Table A14.

Population: Patients with P-ACC-related neurocognitive symptoms
Intervention: Transcranial direct current stimulation (tDCS)
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	Transcranial direct current stimulation (tDCS)		
Cognitive improvement	Relative risk 0.59 (95% CI 0.33 to 1.05) Based on data from 47 participants in 1 study Follow-up 30 days	**667** per 1000	**394** per 1000 Difference: **273 fewer per 1000** (95% CI 447 fewer to 33 more)	**Low** Due to very serious imprecision[a]	tDCS may have little or no difference on cognitive improvement

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A15.

Population: Patients with P-ACC-related olfactory and/or gustatory dysfunction
Intervention: ADAPT-232
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	ADAPT-232		
Olfactory symptoms improvement	Relative risk 0.89 (95% CI 0.79 to 1.01) Based on data from 99 participants in 1 study Follow-up 21 days	**960** per 1000	**854** per 1000 Difference: **106 fewer per 1000** (95% CI 202 fewer to 10 more)	**Low** Due to very serious imprecision[a]	ADAPT-232 may have little or no difference on olfactory symptoms

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A16.

Population: Patients with P-ACC-related olfactory and/or gustatory dysfunction
Intervention: Palmitoylethanolamide + Luteolin
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	Palmitoylethanolamide + Luteolin		
Olfactory symptoms improvement	Relative risk 1.11 (95% CI 0.68 to 1.81) Based on data from 126 participants in 1 study Follow-up 90 days	**368** per 1000	**408** per 1000 Difference: **40 more per 1000** (95% CI 118 fewer to 298 more)	**Low** Due to very serious imprecision[a]	Palmitoylethanolamide + luteolin may have little or no difference on olfactory symptoms improvement

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A17.

Population: Patients with P-ACC-related olfactory and/or gustatory dysfunction
Intervention: Steroids
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Steroids		
Olfactory symptoms improvement	Relative risk: 1.09 (CI 95% 0.83 - 1.44) Based on data from 131 participants in 2 studies Follow up 52 days	**365** per 1000	**398** per 1000 Difference: **33 more per 1000** (CI 95% 62 fewer - 161 more)	**Low** Due to very serious imprecision[1]	Steroids may have little or no difference on olfactory symptoms
Gustatory symptoms improvement	Relative risk: 1.01 (CI 95% 0.67 - 1.53) Based on data from 113 participants in 1 studies Follow up 84 days	**443** per 1000	**447** per 1000 Difference: **4 more per 1000** (CI 95% 146 fewer - 235 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Steroids may have little or no difference on gustatory symptoms

1. **Imprecision: very serious.** Low number of patients, Wide confidence intervals;
2. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients;

Summary of findings Table A18.

Population: Patients with P-ACC-related psychological distress
Intervention: Virtual reality informational video
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	**Absolute effect estimates** Virtual informational video	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Depression improvement	Relative risk 1.21 (95% CI 0.95 to 1.54) Based on data from 89 participants in 1 study Follow-up 90 days	**682** per 1000	**825** per 1000 Difference: **143 more per 1000** (95% CI 34 fewer to 368 more)	**Low** Due to serious risk of bias, Due to serious imprecision[a]	Virtual reality informational video may increase depression improvement
Post-traumatic stress disorder improvement	Relative risk 1.18 (95% CI 0.98 to 1.42) Based on data from 89 participants in 1 study Follow-up 90 days	**773** per 1000	**912** per 1000 Difference: **139 more per 1000** (95% CI 15 fewer to 227 more)	**Low** Due to serious risk of bias, Due to serious imprecision[b]	Virtual reality informational video may increase post-traumatic stress disorder improvement
Psychologic distress improvement	Relative risk 1.49 (95% CI 1.08 to 2.05) Based on data from 89 participants in 1 study Follow-up 90 days	**523** per 1000	**779** per 1000 Difference: **256 more per 1000** (95% CI 42 more to 549 more)	**Low** Due to serious risk of bias, Due to serious imprecision[c]	Virtual reality informational video may increase psychological distress improvement

a. **Risk of bias: serious. Imprecision: serious.** Low number of patients.
b. **Risk of bias: serious. Imprecision: serious.** Low number of patients.
c. **Risk of bias: serious. Imprecision: serious.** Low number of patients.

Summary of findings Table A19.

Population: Patients with PIMS-TS
Intervention: Steroids
Comparator: IVIG

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** IVIG	Steroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Time to discharge time reduction[1]	Relative risk: 1.09 (CI 95% 0.88 - 1.39) Based on data from 75 participants in 1 study Follow up 28	**500** per 1000	**545** per 1000 Difference: **45 more per 1000** (CI 95% 60 fewer - 195 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Steroids may decrease time to discharge
Respiratory support	Relative risk: 0.49 (CI 95% 0.27 - 0.89) Based on data from 75 participants in 1 study Follow up 28	**553** per 1000	**271** per 1000 Difference: **282 fewer per 1000** (CI 95% 404 fewer - 61 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Steroids may decrease respiratory support requirements
Inotropic requirements	Relative risk: 0.68 (CI 95% 0.35 - 1.32) Based on data from 75 participants in 1 study Follow up 28	**395** per 1000	**269** per 1000 Difference: **126 fewer per 1000** (CI 95% 257 fewer - 126 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to very serious imprecision[4]	We are uncertain whether steroids increases or decreases inotropic requirements
Left ventricular fraction deterioration	Relative risk: 0.57 (CI 95% 0.21 - 1.54) Based on data from 75 participants in 1 study Follow up 28	**237** per 1000	**135** per 1000 Difference: **102 fewer per 1000** (CI 95% 187 fewer - 128 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to very serious imprecision[5]	We are uncertain whether steroids increases or decreases LVEF deterioration
Arrhythmia	Relative risk: 2.05 (CI 95% 0.19 - 21.7) Based on data from 75 participants in 1 study Follow up 28	**26** per 1000	**53** per 1000 Difference: **27 more per 1000** (CI 95% 21 fewer - 538 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to very serious imprecision[6]	We are uncertain whether steroids increases or decreases Arrhythmias
Venous thromboembolic events	Relative risk: 0.34 (CI 95% 0.01 - 8.14) Based on data from 75 participants in 1 study Follow up 28	**39** per 1000	**13** per 1000 Difference: **26 fewer per 1000** (CI 95% 39 fewer - 278 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to very serious imprecision[7]	We are uncertain whether steroids increases or decreases VTE

1. Proportion of patients discharged on day 6
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Wide confidence intervals;
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Wide confidence intervals;
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Wide confidence intervals;
5. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Wide confidence intervals;

6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Wide confidence intervals;
7. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Wide confidence intervals;

Summary of findings Table A20.

Population: Patients with COVID-19
Intervention: Metformin to prevent P-ACC
Comparator: SOC

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Metfomin to prevent P-ACC		
P-ACC	Relative risk: 0.59 (CI 95% 0.39 - 0.88) Based on data from 1125 participants in 1 studies Follow up 300 days	**105** per 1000	**62** per 1000 Difference: **43 fewer per 1000** (CI 95% 64 fewer - 13 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Metformin may reduce P-ACC

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients

Summary of findings Table A21.

Population: Patients with COVID-19
Intervention: Ivermectin to prevent P-ACC
Comparator: SOC

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Ivermectin to prevent P-ACC		
P-ACC	Relative risk: 0.99 (CI 95% 0.61 - 1.62) Based on data from 738 participants in 1 studies Follow up 300 days	**105** per 1000	**104** per 1000 Difference: **1 fewer per 1000** (CI 95% 41 fewer - 65 more)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Ivermectin may not reduce P-ACC

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients;

Summary of findings Table A22.

Population: Patients with COVID-19
Intervention: Convalescent plasma to prevent P-ACC
Comparator: SOC

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	CP to prevent P-ACC		
P-ACC	Relative risk: 0.93 (CI 95% 0.77 - 1.12) Based on data from 882 participants in 1 studies Follow up 90 days	**343** per 1000	**319** per 1000 Difference: **24 fewer per 1000** (CI 95% 79 fewer - 41 more)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Convalescent plasma may not reduce P-ACC

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients;

Summary of findings Table A23.

Population: Patients with COVID-19
Intervention: Remdesivir to prevent P-ACC
Comparator: SOC

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Remdesivir to prevent P-ACC		
Mortality	Relative risk: 0.85 (CI 95% 0.25 - 2.83) Based on data from 181 participants in 1 studies Follow up 365 days	**60** per 1000	**51** per 1000 Difference: **9 fewer per 1000** (CI 95% 45 fewer - 110 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision	We are uncertain whether remdesivir to prevent p-acc increases or decreases mortality
P-ACC	Relative risk: 1.06 (CI 95% 0.53 - 2.13) Based on data from 181 participants in 1 studies Follow up 365 days	**145** per 1000	**154** per 1000 Difference: **9 more per 1000** (CI 95% 68 fewer - 164 more)	**Low** Due to serious risk of bias, Due to serious imprecision	Remdesivir may not reduce P-ACC

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** Low number of patients, Wide confidence intervals;
2. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Low number of patients;

This review compiles the evidence on potential therapeutic options for post-COVID-19 condition (PCC). Included are all the identified clinical forms, symptoms and manifestations of PCC for which an intervention was assessed in at least one randomized controlled trial.