Interventions to improve Long COVID symptoms: A systematic review

Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

COVID-19 Evidence Synthesis:

Protocol for interventions to improve long COVID symptoms: A systematic review

28 March 2023

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.

- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.

- **Regulating health services —** Regulating medical exposure to ionising radiation.

- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.

- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.

- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.

- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

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1 Background

1.1 Purpose

As of 28 February 2023 there have been over 750 million laboratory-confirmed COVID-19 cases worldwide.[1] Among people infected with SARS-CoV-2, some will experience long COVID. Although its definition can vary, long COVID (also referred to as post-acute COVID-19, post COVID-19 syndrome, post-acute sequelae of SARS-CoV-2 infection, long-term effects of COVID, and chronic COVID) typically refers to a range of prolonged and persistent symptoms that occur after the acute SARS-CoV-2 infection period.[2, 3] Long COVID can affect several bodily systems, including, but not limited to, the respiratory, cardiovascular, neurological, gastrointestinal, and musculoskeletal systems.[4] Ensuing symptoms can include fatigue and or weakness, breathlessness, impaired usual activity, impaired taste and smell, and depression, among many others,[5] and may have substantial negative physical, mental, social, and economic effects.[5-7]

Long COVID and its underlying mechanisms are still poorly understood as it may affect people regardless of their COVID-19 severity infection or age.[8, 9] Estimates of prevalence vary substantially. A recent meta-analysis of 194 studies (n=735,006) estimated that at least 45% of COVID-19 survivors were experiencing unresolved symptoms approximately four months after infection. However, pooled estimates from this meta-analysis had very high heterogeneity, which was not explained by the study level characteristics of age, the proportion of the sample who were male, follow-up time, or estimated prevalence of 'one or more symptom' in the sample.[5]

Following a request from the Health Service Executive (HSE), HIQA agreed to undertake a review of interventions to improve long COVID symptoms. This protocol details the processes by which HIQA's COVID-19 Evidence Synthesis Team will conduct this review.

1.2 Process outline

This systematic review will adhere to PRISMA guidelines.[10] Six distinct steps in the process, listed below and further detailed in Section 2, will be completed.

1. Develop a research question and formulate a Population, Intervention, Comparator, Outcomes and Study design (PICOS) framework.
2. Search relevant sources.
3. Screen identified documents.
4. Extract data from retrieved studies.
5. Conduct study risk of bias assessments.
6. Summarise study findings.

2 Review process

2.1 Research question

The research question was formulated according to the Population, Intervention, Comparator, Outcomes and Study design (PICOS) framework (Table 2.1). The systematic review seeks to answer the following question:

- What interventions improve long COVID symptoms?

Table 2.1. Population, Intervention, Comparator, Outcomes and Study design (PICOS) criteria

Population	Patients with long COVID, as defined by study investigators. Exclusion criteria: ▪ Signs or symptoms not reasonably attributable to prior SARS-CoV-2 infection. ▪ Insufficient information provided to ascertain inclusion.
Intervention	Any intervention intended to improve long COVID symptoms. Subgroups: ▪ pharmaceutical interventions (for example, monoclonal antibodies and co-enzyme drugs) ▪ non-pharmaceutical interventions (for example, exercise, food supplements, homeopathic medicines, traditional herbal remedies or other therapeutic interventions). Exclusion criteria: ▪ Intervention is not intended to treat long COVID (for example, intervention is intended to treat acute COVID-19 or symptoms resulting from severe COVID-19 complications). ▪ Pre- or post-exposure prophylaxis for COVID-19 or the prevention of long COVID symptoms (for example, administration of the intervention during the acute phase of the disease). ▪ Insufficient information provided to ascertain inclusion.
Comparator	Any comparator (including alternative interventions or placebo) or none for non-controlled trials. Exclusion criteria:

	▪ Studies will not be excluded based on their comparator.
Outcomes	Severity or frequency of long COVID symptoms, including: ▪ pulmonary/respiratory symptoms (for example, breathlessness, dyspnoea and pulmonary function) ▪ energy/fatigue symptoms ▪ mental and cognitive health (for example, anxiety and depressive symptoms and cognitive function) ▪ pain (for example, chest pain and headache) ▪ taste/smell (for example, aguesia and anosmia) ▪ physical functioning and sleep (for example, aerobic capacity, strength and sleep quality) ▪ burden of disease (for example, health-related quality of life, health care usage, and recovery). Exclusion criteria: ▪ Qualitative assessment of outcomes.
Study type	Prospective, interventional studies, including randomised controlled trials, non-randomised controlled trials, and single-arm trials*. Exclusion criteria: ▪ Studies designed to assess the feasibility or tolerability of an intervention rather than its effects on symptoms. ▪ Observational studies. ▪ Case studies. ▪ Retrospective studies. ▪ Animal studies. ▪ Insufficient information provided to ascertain inclusion.

*If sufficient randomised controlled trials are identified, single-arm and non-randomised trials will be excluded.

2.2 Data sources and searches

Electronic searches will be conducted in Medline via EBSCOhost, Embase via Ovid, and CENTRAL via The Cochrane Library. The search strategy for Medline is presented in Appendix 1. Search strategy. Electronic searches will be supplemented by grey literature searches in Clinicaltrials.gov, Cochrane COVID-19 Study Registry, TRIP database, C-19 Living Map - Long COVID 'Segment', and Medrxiv. Recent related reviews[11-14] and a related HIQA report will be screened for relevant studies. Forward and backward citation searching of included studies will be undertaken. Retrieved studies will be de-duplicated in Endnote.

2.3 Study selection

The screening will be undertaken using Covidence software. Inclusion and exclusion criteria are detailed in Table 2.1. First, titles and abstracts of retrieved studies will be screened. Subsequently, full texts of potentially eligible studies will be screened. When full texts are not available, a copy will be requested from the corresponding author. If no response is received, reminder emails will be sent one and two weeks after the initial email. In both phases, two reviewers will screen studies independently. Disagreements will be resolved by discussion or a third reviewer, if necessary. Alerts for redacted studies will be received through Redaction Watch to ensure such studies have not been included. No language restrictions will be applied, although searches will only be conducted in English. When studies are unavailable in English, titles and abstracts will be translated using Google Translate. Full texts of potentially eligible studies will subsequently be translated, also using Google Translate. These translations will be noted as a potential limitation.

2.4 Data extraction

Two reviewers will extract data independently. Disagreements will be resolved by discussion or a third reviewer, if necessary. A standardised data extraction template will be developed and piloted before undertaking data extraction (Appendix 2. Data extraction template). Briefly, data on funding sources, study and patient characteristics, and study outcomes will be extracted. If a paper has not been peer-reviewed, this will be noted. Prior to publishing this review, updated versions of pre-print publications or their associated peer-reviewed manuscript, which have become available since the original search was conducted, will be sought. Any discrepancies in extracted data will be corrected.

2.5 Study risk of bias assessment

Two reviewers will assess study risk of bias independently, and disagreements will be resolved by discussion or a third reviewer, if necessary. Risk of bias for randomised controlled trials will be assessed at the study level using the original Cochrane Risk of Bias tool[15] as opposed to the updated tool (RoB 2)[16] which assesses risk of bias for each outcome at each time point reported within studies. This will limit the previously documented difficulty and demands of RoB 2 which would likely be amplified in this review as it will include studies examining many long COVID symptoms.[17] In addition, using RoB 2, but limiting the assessment to primary outcomes only could result in the omission of potentially useful outcomes. Finally, reporting one risk of bias per study better fits the planned review structure that will include a write-up studies grouped by their interventions rather than outcomes. The Cochrane tool assesses risk of bias in six domains: sequence

generation, allocation concealment, blinding of participants and personnel, incomplete data, and selective reporting.

Risk of bias for other interventions (for example, nonrandomised controlled trials or single arm trials) will be assessed by the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS).[18] RoBANS assesses risk of bias in five domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias.

2.6 Evidence synthesis

The number of records identified, included and excluded will be presented in a PRISMA flow chart.[10] The evidence synthesis may be restricted to high quality studies and or randomised controlled trials if enough of these are identified to develop meaningful advice to the HSE. If the data permit, Hedges' *d* effect sizes will be calculated,[19] meta-analysis will be conducted, heterogeneity assessed, and meta-regression used, as appropriate. If the data do not allow for meta-analysis, as is anticipated due to the expected heterogeneity of included studies, the findings of the included studies will be narratively synthesised. The results will be stratified by pharmaceutical and non-pharmaceutical interventions. If deemed appropriate, the certainty of evidence will be assessed independently by two reviewers using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.[20] The GRADE assessment uses five factors to determine confidence in the body of evidence: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Additionally, registered trials that meet the inclusion criteria but have not been published by the conclusion of the data search will be listed.

3 Quality assurance processes

The review process will be undertaken in accordance with the Health Technology Assessment directorate's Quality Assurance Framework and led by an experienced member of the team. Two senior members of the COVID-19 Evidence Synthesis Team will review the report to ensure its quality and that the correct processes were followed. Additionally, draft outputs from the evidence synthesis will be circulated to HIQA's COVID-19 Expert Advisory Group for review and subsequently presented and discussed at a meeting of the Expert Advisory Group.

4 Review and update

As the understanding of long COVID is continuing to grow, this protocol will be regarded as a live document and may be amended to ensure it reflects any changes made to the outlined processes. Amendments will be captured in the version history.

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Appendix

Appendix 1. Search strategy

Database: Medline Complete via Ebscohost

Search date: 28/02/2023

#	Query	Limiters/Expanders	Results
S17	S10 AND S15	Limiters - Date of Publication: 20201201- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,807
S16	S10 AND S15	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,940
S15	S14 NOT S13	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2,809,692
S14	S11 OR S12	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2,909,253
S13	(MH "Animals") NOT (MH "Humans")	Expanders - Apply equivalent subjects	5,061,258

		Search modes - Boolean/Phrase	
S12	MH "Cohort Studies" OR MH "Longitudinal Studies" OR MH "Prospective Studies" OR MH "Follow Up Studies" OR TI (cohort OR longitudinal OR prospective OR "follow up") N1 (study OR analys* OR design OR method*) OR AB (cohort OR longitudinal OR prospective OR "follow up") N1 (study OR analys* OR design OR method*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,439,536
S11	PT controlled clinical trial OR PT "Randomized Controlled Trial" OR TI trial OR AB trial OR TI placebo* OR TI "single blind*" OR TI "double blind*" OR TI "triple blind*" OR AB placebo* OR AB "single blind*" OR AB "double blind*" OR AB "triple blind*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,692,659
S10	S3 OR S4 OR S5 OR S6 OR S9	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	9,448
S9	S7 AND S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5,670
S8	S1 OR S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	214,849
S7	AB ((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover*" or lasting or continuous* or continual* or continuing* or postacute* or "post acute*" or "long* term*" or "long-term" or "long duration*" or "long last*" or "long standing*" or postinfect* or "post infect*" or postviral* or "post viral*" or postvirus* or "post virus*") N2 (sequela* or illness or symptom* or sign* or indicat* or syndrom* or	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	452,620

	infection*)) OR TI ((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover*" or lasting or continuous* or continual* or continuing* or postacute* or "post acute*" or "long* term*" or "long-term" or "long duration*" or "long last*" or "long standing*" or postinfect* or "post infect*" or postviral* or "post viral*" or postvirus* or "post virus*") N2 (sequela* or illness or symptom* or sign* or indicat* or syndrom* or infection*))		
S6	AB ((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover*" or lasting or continuous* or continual* or continuing* or postacute* or "post acute*" or "long* term*" or "long duration*" or "long last*" or "long standing*" or postinfect* or "post infect*" or postviral* or "post viral*" or postvirus* or "post virus*") N2 (sequela* or illness or symptom* or sign* or indicat* or syndrom* or infection*)) N10 (covid* or coronavirus* or corona* virus* or Cov or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or "severe acute respiratory syndrome*" or Ncov* or "n-cov")) OR TI ((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover*" or lasting or continuous* or continual* or continuing* or postacute* or "post acute*" or "long* term*" or "long duration*" or "long last*" or "long standing*" or postinfect* or "post infect*" or postviral* or "post viral*" or postvirus* or "post virus*") N2 (sequela* or illness or symptom* or sign* or indicat* or syndrom* or infection*)) N10 (covid* or coronavirus* or corona* virus* or Cov or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or "severe acute respiratory syndrome*" or Ncov* or "n-cov"))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5,327
S5	AB (("long haul*" OR longhaul* OR postacute OR "post acute" OR post-acute) N2 (covid19 OR covid-19 OR "sars-cov-2*" OR "sarscov-2*" OR "sarscov2*" OR "sars-cov2*" OR "severe acute respiratory syndrome*" OR ncov* OR "n-cov")) OR TI (("long haul*" OR longhaul* OR postacute OR "post acute" OR post-acute) N2 (covid19 OR covid-19 OR "sars-cov-2*" OR "sarscov-2*" OR "sarscov2*" OR "sars-cov2*" OR "severe acute respiratory syndrome*" OR ncov* OR "n-cov"))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	976

S4	AB (("post covid" or "post-covid-19" or postcovid or "post coronavirus" or postcoronavirus or "post coronovirus" or postcoronovirus or "post sars cov 2" or "post-sars-CoV-2") N2 (syndrome* OR disorder* OR illness* OR sickness* OR disease* OR condition* OR symptom* OR sign* OR feature* OR manifestation*)) OR TI (("post covid" or "post-covid-19" or postcovid or "post coronavirus" or postcoronavirus or "post coronovirus" or postcoronovirus or "post sars cov 2" or "post-sars-CoV-2") N2 (syndrome* OR disorder* OR illness* OR sickness* OR disease* OR condition* OR symptom* OR sign* OR feature* OR manifestation*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,564
S3	(MH "Post-Acute COVID-19 Syndrome")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,665
S2	(MH "SARS-CoV-2")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	148,015
S1	(MH "COVID-19")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	209,405

Appendix 2. Data extraction template

Study characteristics	Patient characteristics	Outcomes
Funding Country Intervention Control Length of follow-up Blinding	Long COVID definition Sample size Age Female	List of author-stated primary and secondary outcomes Findings for review outcomes

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