

**National Institute for Health and
Care Excellence**

COVID-19 rapid guideline: managing the long-term effects of COVID-19

[D] Evidence reviews for interventions

NICE guideline NG188

December 2020

Guideline version (Final)



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**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

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Review question 5: interventions

December 2020

Literature search

NICE's information services team identified relevant evidence through focused evidence searches between 22 and 28 October 2020 (see [search history document](#)). Additional studies were also considered from NICE surveillance up to 28 October 2020. Results from the literature searches and surveillance were screened using their titles and abstracts for relevance against the criteria from the protocol (see [appendix 2](#)). Four reviewers screened titles and abstracts. Having identified the evidence, four reviewers assessed the full text references of potentially relevant evidence to determine whether they met the inclusion criteria for this evidence review. All uncertainties were discussed and referred to an adviser if needed. See [appendix 4](#) for the study flow chart of included studies.

To complement this search, the Healthcare Improvement Scotland knowledge management team conducted a search to identify qualitative evidence to support the questions in this review. See [Managing the long-term effects of COVID-19: the views and experiences of patients, their families and carers](#) for more information. The search for patient experience evidence identified five qualitative studies relevant to the overall review. The themes emerging from these studies were considered alongside the quantitative evidence and included where appropriate. This review will be referred to in this document as "patient lived experience".

Review question 5

What pharmacological and non-pharmacological interventions improve the ongoing physical or mental health symptoms and problems carrying out usual activities, including work, education and leisure, following acute COVID-19?

The review protocol is shown in [appendix 2](#).

Included studies

In total 4104 references were identified through the searches. Of these 505 were included and ordered for full text assessment. A total of 58 references were included for the whole guideline, 2 of which were included for this review. No intervention studies were found and the 2 included studies were rapid reviews; 1 rapid living systematic review, and 1 rapid narrative review with practice recommendations for primary care. See [table 1](#).

Table 1 Included studies for review question 5

Study	Country, study design, dates	Population	Interventions and comparators	Outcomes	Main results
Andrenelli 2020	International, rapid living systematic reviews, September 2020	Inpatients and outpatients with confirmed COVID-19	Rehabilitation of limitations of functioning (disability) due to COVID-19 Any comparators	Outcomes for limitations of functioning	No studies were found on rehabilitation interventions in the post-acute or chronic phases
Greenhalgh 2020a	UK, rapid narrative review and practice recommendations Published August 2020	Patients who have a delayed recovery from an episode of covid-19 that was managed in the community or in a standard hospital ward	Medical management Self-management No comparators reported	Not reported	Recommended medical management: <ul style="list-style-type: none"> • Symptomatic treatment e.g., treating fever with paracetamol, cough with breathing control exercises • Optimise control of long-term conditions • Listening and empathy • Consider antibiotics for secondary infection • Treat specific complications as indicated Recommended self-management: <ul style="list-style-type: none"> • Daily pulse oximetry with safety netting advice • Attention to general health • Rest and relaxation • Self-pacing and gradual increase in exercise if tolerated • Set achievable targets

Key results

No primary research studies were identified. A rapid living systematic review (Andrenelli, 2020) also found no evidence on rehabilitation interventions in the post-acute or chronic phases of COVID-19. Low quality evidence from a rapid narrative review (Greenhalgh 2020a) of indirect evidence proposed self-management and medical management interventions for primary care with additional community mental health support, safety netting and referral. The proposed medical management included listening and empathy, and the need for this was reinforced by the patient lived experience evidence, where acceptance and understanding emerged as a prominent theme of importance to many patients. The patient lived experience data further indicated that providing knowledge and understanding of their condition helped people manage their anxiety.

Strengths and limitations

Please note that GRADE is not used for NICE rapid COVID-19 guidelines. Risk of bias assessment is conducted.

Due to the novelty of the topic and the sparseness of the evidence base, the search was extended to include descriptive and analytic study designs. No primary research studies were identified for the evidence review and this finding was reinforced by the secondary evidence from a rapid living systematic review (Andrenelli 2020), which found no evidence on rehabilitation interventions, and a rapid narrative review (Greenhalgh 2020a) that was limited by indirect evidence from previous coronavirus outbreaks and expert opinion.

Expert panel discussion

This section describes how the expert panel considered the evidence in relation to the recommendations within the guidance.

Relative value of different outcomes

The outcomes the panel expected from the evidence on interventions for the long-term effects of COVID-19 were symptom improvement or worsening, mortality, return to usual activities, quality of life and adverse events. However, in the absence of primary research, none of these outcomes were reported and the secondary COVID-19 rapid evidence review: managing the long-term effects of COVID-19 (December 2020) 7 of 21

evidence was restricted to proposed interventions based on indirect evidence and expert opinion. These interventions informed the panel discussions and reinforced recommendations on management and rehabilitation. Additionally, components of service models that were identified in the related service model evidence review informed the panel's decision making. The main components advocated by the panel were the use of multidisciplinary teams with specialist expertise, individualised interventions beginning with self-management, and the use of both remote and in-person modes of delivery.

Quality of the evidence

The panel noted the lack of evidence on interventions and therefore largely based its recommendations on its own clinical and lived experience.

Trade-off between benefits and harms

The panel expressed concern over the use of interventions to manage short term symptoms that might cause harm in the longer term, indicating the need for the guideline to advise caution over such interventions, including over the counter medicines.

The panel discussed the ongoing debate over self-pacing and graded forms of exercise. The panel considered careful self-pacing of exercise to be an important element of self-management. However, the panel concluded that in the absence of evidence relating to people with ongoing symptoms from COVID-19 it could not make specific recommendations and it agreed to include a research recommendation to determine the effectiveness of exercise interventions for this population.

The panel stated, from their professional experience, that home pulse oximetry can induce anxiety and may not always be accurate, and therefore advised that it should be accompanied by educational materials to be effective. The panel emphasised the need for differentiation in support to address differing symptoms and circumstances, such as difficulty using digital platforms for people with cognitive problems or accessibility issues.

Implementation and resource considerations

The panel highlighted the current resource constraints of pulmonary rehabilitation services and that post COVID-19 syndrome would require additional resources to fund rehabilitation. The panel also expressed concern over the impact on existing services for other conditions and agreed that resources should not be diverted from these services to new COVID-19 rehabilitation services.

Other considerations

The panel agreed that there is a need for the guideline to acknowledge social and financial factors in supporting patient recovery. The panel highlighted that sources of advice and support should include support groups, social prescribing, online forums and apps. This was supported by patient lived experience evidence, which indicated that patients valued these types of interventions. The panel were aware of the online support service YourCOVIDRecovery. Support from other services was also considered to be important, including social care, housing, employment, and advice about financial support. Based on their own experience, the panel agreed on the value of symptom diaries and symptom tracking apps in self-monitoring.

The panel agreed that multidisciplinary rehabilitation teams should work with people to make a personalised plan for their rehabilitation needs, but they emphasised that rehabilitation planning should only happen after checking for symptoms that would need investigating before the person can safely start rehabilitation. The panel agreed on the potential the value of a multidisciplinary approach to rehabilitation, including fatigue management, breathing retraining, and psychological or psychiatric support.

Appendix 1 Methods used to develop the guidance

Please refer to [methods document](#) for details of the methods used to develop the guidance.

Appendix 2 Review protocols

Review question 5: What pharmacological and non-pharmacological interventions improve the ongoing physical or mental health symptoms and problems carrying out usual activities, including work, education and leisure, following acute COVID-19?

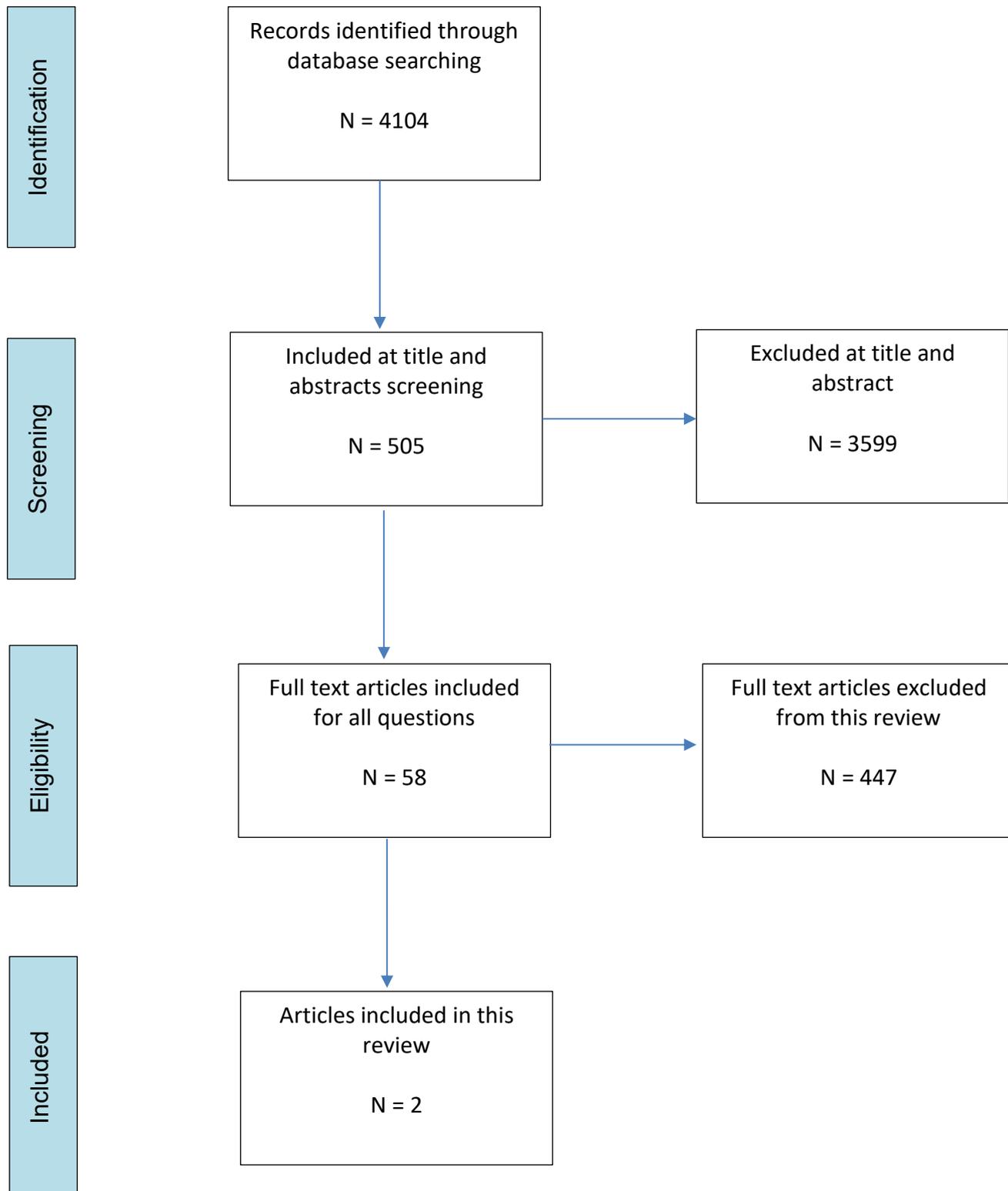
Criteria	Notes
Population	Adults and children who are experiencing new or ongoing symptoms: <ul style="list-style-type: none"> • 4 to 12 weeks from onset of acute COVID-19 • 12 weeks from onset of acute COVID-19
Interventions	<ul style="list-style-type: none"> • Pharmacological interventions • Non-pharmacological interventions For treatment, management (including self-management and rehabilitation) and support
Comparators	Any or no comparator
Outcomes	<ul style="list-style-type: none"> • Symptom improvement (or worsening) • Mortality • Return to usual activities including work, education or leisure • Resumption of (informal) caring arrangements • Quality of life and/or Wellbeing • Adverse events (relating to treatment), e.g. side effects or unintended consequences
Settings	Any
Subgroups	<ul style="list-style-type: none"> • Groups as defined in the EIA for example, age, sex, ethnicity • Diagnosis of COVID-19 (e.g., confirmed, or high clinical suspicion) • Duration of symptoms
Study types	<p>Any</p> <p>The following study design types for this question are preferred. Where these studies are not identified, other study designs will be considered.</p> <ul style="list-style-type: none"> • Systematic reviews of RCTs and observational studies • RCTs • Prospective and retrospective observational studies
Countries	Any
Timepoints	Any
Other exclusions	<ul style="list-style-type: none"> • Management of acute COVID-19 (symptoms experienced for up to 4 weeks) • Management of other conditions with similar features to post-COVID-19 syndrome, for example post-intensive

	<p>care syndrome and myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome (ME/CFS)</p> <ul style="list-style-type: none">• Management of end-organ damage, which already has defined pathways of care.
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Appendix 3 Literature search strategy

Please refer to the [search history record](#) for full details of the search.

Appendix 4 Study flow diagram



Appendix 5 Included studies

Andrenelli E, Negrini F, De Sire A et al. Rehabilitation and COVID-19: a rapid living systematic review 2020 by Cochrane Rehabilitation Field. Update as of September 30th, 2020. European journal of physical and rehabilitation medicine

Greenhalgh, Trisha, Knight, Matthew, A'Court, Christine et al. (2020) Management of post-acute covid-19 in primary care. BMJ 370

Appendix 6 Evidence tables

Andrenelli 2020

Bibliographic reference/s	Andrenelli E, Negrini F, De Sire A et al. Rehabilitation and COVID-19: a rapid living systematic review 2020 by Cochrane Rehabilitation Field. Update as of September 30th, 2020. European journal of physical and rehabilitation medicine
Questions relevant to?	Interventions
Publication status	Published
Study type	Rapid living systematic review
Quality	No evidence identified CASP critical appraisal checklist: Low risk of bias
Objective	to provide an up-to-date overview of recent research relevant to Rehabilitation and COVID-19.
Study date/	30/9/20
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	International: Europe (16 studies), Americas (14), Western pacific (6) and South East Asia (1)
Population (including n)	Inpatients or outpatients with a confirmed diagnosis of COVID-19 with or without comorbidities or disability. 37 studies including case reports, case series, cross sectional studies, historical cohort studies.
Time since acute COVID-19	Thirty-two studies (86.5%) included COVID-19 patients who were assessed in the acute (19 studies) or post-acute phases (13 studies) No studies described patients in the chronic phase of COVID-19. The post-acute and chronic phase was not defined temporally.
Interventions/ Prognostic factors	Rehabilitation of limitations of functioning (disability) of rehabilitation interest (LFRI) due to COVID-19.
Baseline characteristics	Not reported
Inclusion and exclusion criteria	The inclusion criteria were: 1) inpatients or outpatients with a confirmed diagnosis of COVID-19 with or without comorbidities or disability; 2) no age, gender or ethnicity restrictions; 3) all type of health conditions relevant to rehabilitation; 4) all type of rehabilitation interventions compared with any other interventions; 5) all type of diagnostic test or type of evaluation to determine the presence of COVID-19 associated with health conditions related to rehabilitation; 6) all type of outcome measures; and 7) English language. Studies addressing other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)) were excluded. Expert opinions and all papers not reporting patients' data were excluded; secondary research papers (like systematic and scoping reviews) and expert literature interpretation (guidelines and consensus papers) were also excluded.
Follow up	Not reported

Main results	<p>Due to the heterogeneity of published studies, a meta-analysis was not appropriate, thus the results are described qualitatively.</p> <p>A total of 36 studies were included. The quality of evidence remains low. Most studies (78.4%) were Level 4 (15 case reports, 7 case series, and 7 historical cohort), whereas the remaining 8 papers (21.6%) were Level 3 (4 cohort and 4 cross sectional studies). There are no published RCTs or QRCTs as yet.</p> <p>Just one study dealt with rehabilitation interventions regarding COVID-19, and two discussed reorganisation of rehabilitative services. No studies were found on rehabilitation interventions in the post-acute or chronic phases.</p> <p>Most studies describe subjects in the acute phase (51.4%) or post-acute phase (35%). No studies described patients in the chronic phase. The long-term consequences and prognosis of neurological, respiratory, cardiac damage incurred during COVID-19 are unknown.</p> <p>In the sub-acute phase, surveillance of previously detected abnormalities is important to follow the recovery or the progression of disease using validated outcome measures that are sensitive to change in this phase. The impact of COVID-19 on patients' daily lives is substantial, including for non-hospitalized patients with mild COVID-19, due to the persistence of non-specific symptoms like fatigue, muscle weakness, sleeping problems, and pain. Moreover, the authors caution that a series of complications can occur in the recovery period or even after discharge, such as post-acute oropharyngeal dysphagia, refractory status epilepticus, herpes zoster, cognitive decline and acute massive pulmonary embolism. The subjects most at risk are those with severe illness, pre-existing risk factors and longer length of ICU stay.</p> <p>Studies with higher levels of evidence regarding the efficacy of interventions, long-term monitoring, or new organisation models are lacking.</p>
Comments (e.g. source of funding, statistical analysis, any major limitations or issues with studies)	<p>The topics addressed in main research questions were: 1. epidemiology of "Limitations of functioning (disability) of rehabilitation interest (LFRI) due to COVID-19; 2. evidence on rehabilitation for LFRI due to COVID-19 at the individual level (micro-level); 3. evidence on rehabilitation for LFRI due to COVID-19 at service level (meso-level) and 4. evidence on rehabilitation for LFRI due to COVID-19 at system level (macro-level).</p> <p>The timepoints acute phase, post-acute and chronic phase were not defined.</p>
Additional references	<p>Relevant studies considered in evidence review:</p> <p>Cavalagli A, Peiti G, Conti C, Penati R, Vavassori F, Taveggia G. Cranial nerves impairment in postacute oropharyngeal dysphagia after COVID19: a case report. Eur J Phys Rehabil Med. Published online 2020. doi:10.23736/S1973-9087.20.06452-7</p> <p>Nakayama A, Takayama N, Kobayashi M, et al. Remote cardiac rehabilitation is a good alternative of outpatient cardiac rehabilitation in the COVID19 era. Environ Health Prev Med. Published online 2020. doi:10.1186/s12199-020-00885-2</p> <p>Stierli S, Buss I, Redecker H, Et Al. Insights From An Interprofessional Post-Covid19 Rehabilitation Unit: A Speech And Language Therapy And Respiratory Medicine Perspective. J Rehabil Med Stiftelsen Rehabiliterings information. Published online 2020. doi:10.2340/16501977-2735</p>

Greenhalgh 2020

Bibliographic reference/s	Greenhalgh, Trisha, Knight, Matthew, A'Court, Christine et al. (2020) Management of post-acute covid-19 in primary care. BMJ 370
Questions relevant to?	Risk factors, signs and symptoms, investigations, interventions, referral
Publication status	Published
Study type	Narrative review and expert opinion
Quality	Low quality evidence CASP critical appraisal checklist: High risk of bias
Objective	This article provides a practice guide for primary care clinicians, relating to the patient who has a delayed recovery from an episode of covid-19 that was managed in the community or in a standard hospital ward.
Study date	11/8/20
COVID-19 prevalence (high/low) if reported	Not reported
Country/ Setting	International/primary care
Population (including n)	Patients who have a delayed recovery from an episode of covid-19 that was managed in the community or in a standard hospital ward.
Time since acute COVID-19	for the purposes of the article the authors define post-acute covid-19 as extending beyond three weeks from the onset of first symptoms and chronic covid-19 as extending beyond 12 weeks.
Interventions/ Prognostic factors	Medical and self-management (see main recommendations)
Baseline characteristics	N/A
Inclusion and exclusion criteria	Inclusion: patients who have a delayed recovery from an episode of covid-19 that was managed in the community or in a standard hospital ward.
Follow up	N/A but cites advice from British Thoracic Society guidance on follow-up of covid-19 patients who have had a significant respiratory illness proposes community follow-up with a chest x ray at 12 weeks and referral for new, persistent, or progressive symptoms.
Main recommendations	<p>Recommended clinical assessment:</p> <ul style="list-style-type: none"> • Full history from date of first symptoms • Nature and severity of current symptoms • Examination e.g. temperature, heart rate and rhythm, blood pressure, respiratory examination, functional status, pulse oximetry, clinical testing if indicated; <p>Recommended Investigations if indicated:</p> <ul style="list-style-type: none"> • Blood tests should be ordered selectively and for specific clinical indications after a careful history and examination; the patient may not need any. • Anaemia should be excluded in the breathless patient. • Lymphopenia is a feature of severe, acute covid-19. • Elevated biomarkers may include C reactive protein (for example, acute infection), white cell count (infection or inflammatory response), natriuretic peptides (for example, heart failure), ferritin (inflammation and continuing prothrombotic state), troponin (acute coronary syndrome or myocarditis) and D-dimer (thromboembolic disease).

	<p>Troponin and D-dimer tests may be falsely positive, but a negative result can reduce clinical uncertainty.</p> <ul style="list-style-type: none"> • Further research is likely to refine the indications for, and interpretation of, diagnostic and monitoring tests in follow-up of covid-19. • For patients who were not admitted to intensive care, British Thoracic Society guidance on follow-up of covid-19 patients who have had a significant respiratory illness proposes community follow-up with a chest x ray at 12 weeks and referral for new, persistent, or progressive symptoms. For those with evidence of lung damage (such as persistent abnormal chest x ray and oximeter readings), referral to a respiratory service is recommended. • subsequent early referral to pulmonary rehabilitation probably aids recovery. <p>Recommended medical management:</p> <ul style="list-style-type: none"> • Symptomatic treatment e.g. treating fever with paracetamol, cough with breathing control exercises • Optimise control of long-term conditions • Listening and empathy • Consider antibiotics for secondary infection • Treat specific complications as indicated <p>Recommended self-management:</p> <ul style="list-style-type: none"> • Daily pulse oximetry and safety netting advice • Attention to general health • Rest and relaxation • Self-pacing and gradual increase in exercise if tolerated • Set achievable targets <p>Recommended safety netting and referral:</p> <ul style="list-style-type: none"> • The patient should seek medical advice if concerned e.g. worsening breathlessness, PaO₂<96%, unexplained chest pain, new confusion, focal weakness. • Specialist referral may be indicated based on clinical findings e.g.: <ul style="list-style-type: none"> ○ Respiratory – if suspected pulmonary embolism or severe pneumonia ○ Cardiology – if suspected myocardial infarction, pericarditis, myocarditis or new heart failure ○ Neurology – if suspected neurovascular or acute neurological event.
<p>Comments (e.g. source of funding, statistical analysis, any major limitations or issues with studies)</p>	<p>The authors used a pragmatic approach based on indirect evidence from SARS and MERS, early editorials and consensus-based guidance on COVID-19, a living systematic review, early reports of telerehabilitation (support and exercise via video link), and their own clinical experience.</p> <p>Limitations: no direct evidence was identified.</p>
<p>Additional references</p>	

Appendix 7 Excluded studies

Please refer to the full list of [excluded studies](#) for this guideline.

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