NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

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

Methods document for 2021 update

NICE guideline NG188

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Guideline version (Final)

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

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Development

This guideline was developed and updated by NICE, SIGN and the RCGP using the methods and process in NICE's interim process and methods for guidelines developed in response to health and social care emergencies.

Advisory panel

NICE set up an expert advisory panel including representatives from relevant medical specialties with direct experience in the long-term effects of COVID-19 and people with lived experience of the long-term effects of COVID-19. The panel developed new content, provided ongoing advice for surveillance and assisted with updates to recommendations.

Declarations of interest

The expert advisory panel's declarations of interest (DOI) were recorded according to NICE's policy on declaring and managing interests for advisory committees. DOIs were reviewed on an ongoing basis and the DOI registry updated as needed. For a list of panel members and corresponding DOI registry for this guideline, see NICE's guideline page on managing the long-term effects of COVID-19.

All NICE staff are asked to declare all interests in line with NICE's policy on declaring and managing interests for board members and employees. If a member of the NICE internal development team is conflicted, they are not permitted to help in developing that particular topic.

Scope development

The original scope was agreed in October 2020. As part of NICE's, SIGN's and the RCGP's commitment to keep the review living and the scope up to date, the scope was reviewed in April 2021. For this review, all of the relevant evidence identified through COVID-19 surveillance since publishing NICE's guideline on managing the long-term effects of COVID-19 was assessed for

its effect on the current guidance. A targeted stakeholder workshop was held in June 2021 in which stakeholder views on the current scope, guideline and evidence base were sought. The scope was updated in light of stakeholder feedback, and was refined and agreed on by the expert advisory panel. Additional review questions were developed to address any new themes outlined in the scope.

See the current scope of this guideline.

Equality impact assessment

The impact on equality was assessed during guidance development according to NICE's manual on developing guidelines. Potential equality issues identified were discussed with the expert advisory panel to ensure they were addressed, if appropriate. Equality issues are reassessed with the expert advisory panel during updates, and new issues are added to the equality impact assessment when identified.

See equalities considerations for details about the equality impact assessment.

Developing review questions

The review questions developed for this guideline were based on the key areas identified in the updated guideline scope. They were drafted by the NICE team, and refined and validated by the guideline panel.

Literature searches, critical appraisals and evidence reviews were completed for all review questions.

Identifying the evidence

Searching for evidence

There was an evidence search for each review question using NICE's interim process and methods for guidelines developed in response to health and social care emergencies.

For the new key questions listed in the scope, full literature searches were done if it was deemed that these areas would not be picked up from the master surveillance search, for example, for qualitative questions. Results from the searches were screened against the relevant review protocol. All search strategies are available on request.

Expert testimony

If limited or no relevant studies were found on a key question, the panel could request expert testimony or expert evidence to be presented. This was to help them make recommendations on an identified evidence gap. A call for evidence was not appropriate because of the short development time, and very specific knowledge and expertise that was needed. Expert witnesses were needed for the areas of rehabilitation, vaccines and managing the long-term effects of COVID-19 in people under 18. The experts were chosen based on their knowledge, skills and experience in these areas, as well as their involvement with active research in this area. Expert witnesses were asked specific questions to answer in their testimony. A summary of each expert testimony was recorded in a standard form and can be found in the evidence reviews . When considering expert testimony, the panel considered the applicability, validity and consistency (when there is more than 1 testimony on a subject) of the testimonies. When recommendations are wholly or partly based on expert testimony, the evidence to decision and rationales of relevant recommendations set out the panel considerations of the expert testimony.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by stakeholders or expert panel members) were uploaded into EPPI reviewer software (version 5) and deduplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. Ten per cent of the abstracts were reviewed by 2 reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies.

For the review questions on risk factors and the prevalence of symptoms, because of the high volume of primary evidence in these areas, these additional selection criteria were applied:

- highest quality systematic reviews published in 2021 covering all signs, symptoms and risk factors
- large primary studies (n more than 10,000) not covered by included systematic reviews.

Note that this approach did not apply to children and young people, for which a separate evidence review was done without the additional selection criteria. This was because of the lack of evidence in this area.

This approach was approved by the expert advisory panel and follows NICE's interim process and methods for guidelines developed in response to health and social care emergencies. The rationale for refining the approach from the original review protocol was that important primary studies should be captured by the systematic reviews, which could be supplemented by large primary studies published subsequently. Studies of larger sample sizes were prioritised as being more representative of the general population. From the studies identified, the larger studies sampled over 10,000 people while smaller studies were clustered below this number.

Reviewing the evidence

Living review approach

Recommendations were considered up to date and no further review was done for areas:

- in which evidence supported current recommendations
- that were not identified as priorities for update at the targeted stakeholder workshop.

Studies that were not considered robust enough to support a revision to a recommendation have been retained for future consideration. This is if any further confirmatory evidence is identified.

Evidence was reviewed for areas in which there was:

- new evidence that affected current recommendations
- stakeholder feedback indicating that recommendations needed updating.

When evidence was assessed as having no effect on current recommendations, expert testimony or expert evidence was sought.

Methods of combining evidence

Data synthesis for intervention studies

When possible, meta-analyses are done to combine the results of quantitative studies for each outcome. When there are 2 treatment alternatives, pairwise meta-analysis is used to compare interventions. Network meta-analysis has not been used in this guideline.

Data synthesis for association data

In this guideline, association data is defined as measures of association between 1 or more factors (a single variable or a group of variables) and an outcome variable (when the data is not reported in terms of outcome classification, that is, diagnostic or predictive accuracy). Examples could include (but were not limited to) data assessing the association between variables and:

- diagnosis (diagnostic association studies)
- a future outcome (prognostic association studies).

Ideally, data is reported as hazard ratios (if measured over time), or odds ratios or risk ratios (if measured at a specific time point).

If hazard ratios, and odds ratios or risk ratios are reported, the same methods for meta-analysis of odds ratios and relative risks are used. This is described in the section on data synthesis for intervention studies. When these

measures are not reported, the approach to reporting is agreed with NICE staff with responsibility for quality assurance.

Data synthesis for qualitative reviews

SIGN reviewed the qualitative evidence for the initial guideline and first update. Relevance for the included studies was established via the exclusion and inclusion criteria agreed within the scoping process. The included studies were critically appraised using the Critical Appraisal Skills Programme (CASP) qualitative checklist.

A full thematic synthesis was not done because of the limited amount of relevant information available, but key themes were identified and grouped into concepts. These concepts were presented against the review questions, for example, what people's experiences of symptoms or investigations were. They were also supported by quotes from the data.

Appraising the quality of evidence

Intervention studies (relative effect estimates)

Randomised controlled trials and quasi-randomised controlled trials are quality assessed using the Cochrane Risk of Bias Tool. Non-randomised controlled trials and cohort studies are quality assessed using the ROBINS-I tool. Other study types (for example, controlled before and after studies) are assessed using the preferred option specified in NICE's guidelines manual 2018 (appendix H).

GRADE for intervention studies analysed using pairwise analysis

GRADE is used to assess the quality of evidence for the outcomes specified in the review protocol. Outcomes from randomised controlled trials, non-randomised controlled trials and cohort studies (which are quality assessed using the Cochrane Risk of Bias Tool or ROBINS-I) are initially rated as high quality. Data from other study types is initially rated as low quality. The quality of the evidence for each outcome is downgraded or not from this initial point.

Association studies

Individual prognostic studies presenting data on association are quality assessed using the Quality in Prognostic Studies (QUIPS) checklist. Other cohort and case-control studies are quality assessed using the CASP cohort study checklist and CASP case-control checklist respectively. Individual cross-sectional studies are quality assessed using the Joanna Briggs Institute critical appraisal checklist for analytical cross-sectional studies (2016). This contains 8 questions covering: inclusion criteria, description of the sample, measures of exposure, measures of outcomes, confounding factors and statistical analysis.

Modified GRADE for association data

GRADE has not been developed for use with association studies, so a modified approach is applied using the GRADE framework. Data from cohort, cross-sectional and case-control studies is initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point.

Qualitative studies

Individual qualitative studies are quality assessed using the CASP qualitative checklist to consider appropriateness of the methodology applied, validity and relevance to the key question. GRADE CERQual (Confidence in the Evidence from Reviews of Qualitative Research) is only used if there is sufficient evidence.

Cost effectiveness

Because of the urgency for publishing guidance on long-term effects of COVID-19, no health economic analyses have been done.

Developing recommendations

Recommendations were developed or updated based on the expert advisory panel's discussions of:

- the overall quality of the evidence or confidence in the expert opinion

- the trade-off between benefits and harms
- the impact on equity and equality
- the feasibility of implementation (for example, resources, capacity, settings and acceptability).

Research recommendations

Research recommendations were developed by the expert advisory panel when:

- there was a lack of evidence
- the evidence was uncertain.

Quality assurance

Pragmatic checks and review were done iteratively throughout guideline development and during updates by NICE and SIGN staff with responsibility for quality assurance.

Consultation

Final recommendations were ratified by the expert advisory panel and external stakeholders through a targeted peer-review process. A range of stakeholders were invited to take part, including relevant national professional, and patient or carer groups.

NICE staff collated all comments from stakeholders, so the independent advisory expert panel could consider them. The panel then advised on changes to the recommendation(s) and responses to stakeholder comments. Comments from stakeholders were grouped into themes. Thematic responses were provided to address these themes, instead of responding to individual comments.

All stakeholder comments and thematic responses are available on the NICE guideline page on managing the long-term effects of COVID-19.

Sign off

NICE's guidance executive sign off the guideline, either when new recommendations are published or when recommendations are updated.

Surveillance and future updates

From inception, guideline recommendations were maintained using a continuous 'living' surveillance approach. This ensures that recommendations are updated continuously to reflect changes in:

- the evidence base
- clinical or healthcare practice
- the health and social care system, and government policy.

Living surveillance uses a multifactorial approach to identify 'triggers' for update. This approach includes:

- identifying studies relevant to the scope through weekly evidence searches
- looking at relevant professional guidance in the area
- intelligence gathering, including feedback from the broader health and social care system
- monitoring ongoing research and checking for publication of these ongoing studies regularly.

Surveillance decisions and outcomes are based on continual assessment of the impact of all the new evidence and intelligence that has been identified. There are 4 possible surveillance outcomes:

No update: recommendations will not be updated if new evidence or intelligence does not suggest that any changes are needed.

Refresh of the recommendations: this involves simple editorial changes that improve the usability of the recommendations without changing the intent, or correction of factual errors.

Rapid update of the recommendations: the recommendations could be updated if changes are needed (for example, new evidence emerges). Examples of updates include:

- covering additional populations or settings
- addressing new review questions
- changes to the original review questions, which mean a new search of the evidence is needed
- when new evidence contradicts existing recommendations.

Withdrawal of recommendations: recommendations may be withdrawn if:

- they are no longer needed, for example, because service delivery has changed (such as normal services resuming) or the recommendations are likely to have limited relevance because of changes in context
- there are safety issues (for example, there is evidence of harm to people using the service)
- the recommendations are duplicated somewhere else (for example, if the recommendations are merged with another guideline).

From March 2024, this guideline will be retired from living mode and will undergo surveillance and updates in line with Chapter 13 Ensuring that published guidelines are current and accurate in the Developing NICE Guidelines manual.

Funding

NICE is an executive non-departmental public body sponsored by the Department of Health and Social Care.

A range of organisations, including the Department of Health and Social Care, arms-length bodies, professional associations, and voluntary and community sector groups are invited to become stakeholders. Stakeholders review and comment on draft recommendations as part of a targeted peer review. Stakeholders do not contribute to the systematic review and evidence appraisal process, or determine the final wording of recommendations.