NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COVID-19 rapid guideline: managing the long-term effects of COVID-19 (NG188)

Methods

December 2020

Development of the guideline

Remit

NHS England and the Chief Medical Officer of the Scottish Government asked NICE and the Scottish Intercollegiate Guidelines Network (SIGN) to develop a guideline on the long-term effects of COVID-19. This UK-wide guideline is being developed collaboratively by NICE, SIGN and the Royal College of General Practitioners (RCGP). We acknowledge that there is still uncertainty in what is known about the long-term effects of COVID-19. Therefore, this guideline is being developed using a 'living' approach, which means that targeted areas of the guideline (including the case definition) will be continuously monitored for changes and updated in response to a developing and emerging evidence base.

The guideline scope sets out the areas covered by the guideline.

Methods

This guideline was developed in accordance with the process set out in NICE's interim process and methods for guidelines developed in response to health and social care emergencies.

This document sets out in detail the methods we used to identify and review the evidence and develop the recommendations in the guideline.

The methodological approach taken for the review of the evidence was informed not only by the uncertainty about how to treat the long-term effects of this new and emerging condition, but also about how people experience the condition. In order to create useful guidance in this context, there was a need to understand better not only what interventions might work for this population, but importantly questions that are not always asked in health guideline development, such as what the condition is, who the population is and how their experiences might inform the development of new service models.

As the next sections describe in more detail, the evidence generated by the review questions was used as part of a convergent mixed methods approach (see Stern C, Lizarondo L, Carrier J et al (2020) Methodological guidance for the conduct of mixed methods systematic reviews. JBI Evidence Synthesis 18 (10): 2108–2118). This enabled the panel to explore how far people's experiences in the qualitative data supported or challenged the limited quantitative data and develop a fuller understanding of not only how healthcare might support people experiencing the long-term effects of COVID-19, but also begin to determine what the condition is and how it is experienced.

Developing the review questions and outcomes

The 9 review questions developed for this guideline were based on the key areas identified in the guideline scope. Review questions to cover these key areas were drafted by the NICE COVID-19 development team in conjunction with SIGN and the RCGP. The review questions included a question exploring patient experience of the long-term effects of COVID-19. As part of the mixed methods approach the patient experience review question was used to provide further evidence to explore other review questions more fully. The review questions were consulted on with targeted stakeholders and refined by the guideline panel.

The review questions were based on the framework of population, intervention, comparator and outcome (PICO). This framework was modified where needed for

different types of questions, such as the question on patient lived experience, which used a population, factors of interest and outcomes framework.

Searching the literature

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. One search was undertaken that covered all quantitative review questions. Databases were searched using relevant subject headings and free-text terms. The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage. Searches were not restricted according to date, language or study type, with the exception of letters and editorials. Studies published in languages other than English were not reviewed.

Searches were conducted in MEDLINE, Embase, CINAHL, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL) and PsycINFO. Web-based COVID-19 collections were also searched, including the Cochrane COVID-19 Study Register, Epistemonikos and the WHO COVID-19 database. Pre-prints were obtained from searching the COVID-19 sections of bioRxiv and medRxiv. Further sources included reference checking, scoping searches and surveillance screening. Search dates were 22 to 28 October 2020. Searches were not re-run after this date and no further studies published after this date were included prior to the publication of the guideline due to the short timescales for development, although new evidence was monitored for any impact through weekly surveillance searching.

Search strategies were quality assured by cross checking reference lists of highly relevant papers, analysing search strategies in other reviews and asking panel members to highlight any additional studies. Searches were quality assured by a second information specialist before being run. All translated search strategies were peer reviewed to ensure their accuracy. Full details of the search strategies are in the search record.

Healthcare Improvement Scotland's knowledge management team conducted a separate search to identify the relevant qualitative evidence and develop the evidence review on the views and experiences of patients, their families and carers.

Real-world evidence was presented to the panel for consideration for the review questions on prevalence. This evidence used data from the COVID-19 symptom tracker mobile application (Zoe app). For more details see the section in this document on real-world evidence and evidence reviews 2 and 3: prevalence.

Reviewing published research evidence

Inclusion and exclusion criteria

Inclusion or exclusion of studies was based on the criteria defined in the review protocols (see appendix 2 of the evidence reviews for details).

Types of studies

Depending on the evidence available, the following study types were considered for review:

- systematic reviews of randomised controlled trials (RCTs) or observational studies
- RCTs
- prospective and retrospective observational studies
- descriptive studies; case series and case reports
- mixed method study designs.

Full literature searches, evidence tables (including risk of bias assessment) for all included studies, tables of studies excluded at full text with reasons for exclusion and evidence reviews were completed for all review questions.

Combining published evidence: data synthesis

The published quantitative evidence identified was limited and did not allow for pooling data, so meta-analysis was not undertaken. Narrative synthesis was carried out to report the key findings from included studies. Where possible, findings from the studies were grouped to enable better interpretation of the evidence.

SIGN undertook a review of the qualitative evidence. The emergent themes from an inductive analysis of the data were presented against the review questions, for example what people's experiences of symptoms or investigations were.

Both the quantitative and qualitative published data were presented at each panel meeting when relevant for a review question, identifying where the qualitative data supported, challenged or provided additional information to the quantitative data.

Appraising the quality of evidence

Critical appraisal of the quantitative published evidence was undertaken using appropriate risk-of-bias checklists as listed in the section on appraisal checklists, evidence tables, GRADE and economic profiles in the NICE guidelines manual and described below:

- cohort studies: the CASP cohort study checklist was used instead of the NICE preferred tool (Cochrane ROBINS-I) because most cohort studies did not have a control group.
- case–control studies: the CASP case–control checklist
- cross-sectional studies: the JBI checklist for cross-sectional studies
- case series: theJBI checklist for case series was used instead of the NICE preferred tool (IHE checklist)because of due to time constraints
- systematic reviews: the CASP systematic review checklist was used instead of the NICE preferred tool (ROBIS) because of time constraints.

Each individual study was classified into one of 3 groups:

- low risk of bias – the true effect size for the study is likely to be close to the estimated effect size.
- moderate risk of bias – there is a possibility the true effect size for the study is substantially different to the estimated effect size.
- high risk of bias – it is likely the true effect size for the study is substantially different to the estimated effect size.

GRADE was not used for this guideline, in line with NICE's interim process and methods for guidelines developed in response to health and social care emergencies. The quality of the evidence was conveyed at panel meetings by discussing risk of bias, the directness and generalisability of the evidence and the consistency of findings.

Real-world evidence

Real-world evidence was presented to the panel for consideration for the review questions on prevalence. This evidence used data from the COVID-19 symptom tracker mobile application (Zoe app), which was designed by the scientific/medical team at King's College London, Guys and St Thomas' Hospitals, in partnership with ZOE Global Ltd. This app was first released in March 2020, and allows users to self-report their symptoms. The data collected by this app is hosted within the SAIL data bank. The NICE team gained access to this data in November 2020. The analysis was carried out in SAIL data bank analytics environment using R and SQL. Formal quality assessment of the data was not carried out because of time constraints.

Expert testimony

No published studies were identified for review question 8 on service delivery ('what components should be included in a service model for the delivery of services to people with post-COVID-19 syndrome?'). In line with section 3.5 of the NICE guidelines manual, the panel agreed that expert testimony could potentially help address this gap in evidence, since the panel were aware of a small number of new innovative service models that seek to support this population. The panel identified potential experts from those services and they were invited to provide expert testimony for a panel meeting. The testimony was presented to the panel and written up by the developer. The final summary report was agreed with the expert after the meeting.

Cost-effectiveness evidence

Economic evidence was not considered for this guideline and de-novo health economic modelling was not carried out. A resource impact statement has been published alongside the guideline.

Developing recommendations

Over the course of the guideline development process, the panel were presented with summaries of the quantitative, qualitative and real-world evidence and expert testimony, and a quality assessment of the evidence provided. Recommendations were drafted on the basis of the panel's interpretation of the available evidence and clinical experience. When making recommendations, the panel took into account the relative value of different outcomes, the quality of the evidence, the trade-off between benefits and harms, and implementation and resource considerations. The panel were also mindful of the need to develop a UK-wide guideline and took into account potential differences in the devolved nations.

The main considerations specific to each recommendation are outlined in the expert panel discussion section for each evidence review and in the rationales in the guideline.

Research recommendations

When areas were identified for which evidence was lacking, the panel considered making recommendations for future research. Decisions about the inclusion of research recommendations were based on factors including:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance.

Validating the guideline

This guideline was subject to a targeted stakeholder consultation lasting 1 week. Quality assurance checks on both the guideline and evidence reviews by NICE and SIGN staff with responsibility for quality assurance were conducted and the guideline

was signed off by senior members of the development teams at NICE, SIGN and the RCGP.

See the NICE website for stakeholder comments on the draft guidance divided into themes, the developers' responses to the comments and the full list of comments.

Declarations of interest

Declarations of interest were recorded according to the 2019 NICE conflicts of interest policy.