National Essential Medicines List Committee on Covid-19 Therapeutics Terms Of Reference

15 SEPTEMBER 2021 VERSION 6.0

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Abbreviations

Covid-19	-	Coronavirus Disease 2019
EML	-	Essential Medicine List
HTA	-	Health Technology Assessment
IMT	-	Incident Management Team
MAC	-	Ministerial Advisory Committee
NDoH	-	National Department of Health
NEMLC	-	National Essential Medicines List Committee
PICO	-	Population, Intervention/s, Control, and Outcomes (eligibility criteria)
STG	-	Standard Treatment Guideline(s)
WHO	-	World Health Organization

Introduction

Outbreaks of emerging and re-emerging infectious diseases confer a direct threat to human health, the integrity of our health system, and the national and global economy. Like the influenza pandemics of 1918 and 2009, and epidemics of Ebola Virus Disease (2014), SARS (2002), and MERS (2012), the novel coronavirus SARS-CoV-2 now causing a pandemic of Coronavirus Disease-2019 (Covid-19) focuses our attention on the inter-sectoral, multidisciplinary response required to respond to Covid-19 and the lessons that can be learnt for a future pandemic.

Purpose and Scope

The National Essential Medicines List Committee (NEMLC) on COVID-19 Therapeutics replaces the previous NEMLC COVID-19 Therapeutic Guidelines Subcommittee and is now constituted as a separate ministerially appointed advisory Committee (from 24 August 2021). This Committee is tasked with providing specific patient-focused evidence-based recommendations to support the inclusion of selected medicines in the *Clinical Management of Suspected or Confirmed Covid-19 Disease Guideline*. This guideline applies to situations where guidance is lacking from standard management of similar clinical conditions (e.g. pneumonia, severe acute respiratory distress) already recommended in the current NEMLC-approved Standard Treatment Guidelines (STGs) and Essential Medicines List (EML). Recommendations will be provided in a rapid medicine review format, based on the principles of evidence-based medicine and the approach used by NEMLC.

The Committee may also, in consultation with the chairperson of the Clinical Guideline Writing Committee on Covid-19 and the Lead of the Clinical Care work stream of the Incident Management Team (IMT) of the National Department of Health (NDoH), provide input regarding:

- Therapeutic agents to be prioritised for rapid review to inform the clinical management guidelines;
- Information and issues which require intervention by the South African Health Products Regulatory Authority;
- Recommendations to clinicians about therapeutic interventions under investigation in clinical trials; and

- Recommendations on other issues that emerge during the Covid-19 epidemic.

Authority to act

The Committee provides recommendations on COVID-19 medicines to the Executive Management of the National Department of Health, Ministerial Advisory Committee on COVID-19, and the Clinical Guideline Writing Committee on Covid-19 and does not have any delegated powers to act on behalf of, or to commit, the Government to any actions.

The Chairperson and the Vice-chairperson of the Committee will either be the standing or previous Chairperson and Vice-chairperson of NEMLC or be appointed by the Committee. The Chairperson will appoint a lead and co-lead, who will contribute to the development and updating of the *Clinical Management of Suspected or Confirmed Covid-19 Disease Guideline,* as required. The lead and co-lead will also liaise with, and share rapid evidence reviews with the Clinical Guideline Writing Committee on Covid-19. The NEMLC Committee on COVID-19 Therapeutics will be dissolved once the Clinical Guideline Writing Committee on Covid-19 is dissolved.

Membership

The NEMLC on COVID-19 Therapeutics, comprises current or previous members of the ministerially- appointed NEMLC, members of the ministerially-appointed Expert Review Committees, and members who are not appointed to the NEMLC (including stakeholders with expertise in evidence-based medicine and representation from the national health products regulatory authority). Non-members may be invited to attend meetings and provide presentations as required. Attendance must be approved by the Chairperson of the Committee prior to the meeting. The process for the management of conflict of interest and confidentiality will follow the standard NEMLC processes.

Members of the Committee are participants in their individual capacity and do not represent any constituency, organisation or sector. The recommendations of the NEMLC on COVID-19 Therapeutics will be shared with the current NEMLC for comment. Members have a duty to act honestly and in good faith and to exercise skill, care and diligence in carrying out their duties and not make improper use of information. Members are subject to all of the applicable provisions and procedures surrounding conflict of interest and confidentiality, as per the standard NEMLC process.

Members **may not** nominate representatives to attend meetings in their absence. Members may not allow non-members to listen to or attend the meetings unless approved by the Chairperson.

Code of conduct

Members are expected to:

- avail themselves for meetings, punctually and for the whole of the scheduled meeting time;
- indicate their failure to attend any meeting in writing to the secretariat, in good time with the reason as to why they were unable to attend;

- act with the highest professional and ethical standards at all times;
- contribute to debate in an informed and rational way and take decisions solely in the interest of the public;
- regard the views expressed by individual members of the Committee and recommendations as strictly confidential;
- respect and value each member's perspective and contribution;
- make decisions together and take joint responsibility for decisions taken; and
- be informed and prepared for the meeting by reading the agenda and papers.

Under no circumstances may an individual member, other than the Chairperson, officially represent the views and decisions of the Committee, unless authorised by the Chairperson or the National Department of Health.

Publishing of ratified rapid reviews or pertaining to the rapid review process (e.g. presentations, journal articles, webinars, etc.) requires permission from the National Department of Health. The NEML MAC on COVID-19 Therapeutics will be duly acknowledged, and an opportunity to contribute to the publication will be provided to other Committee members to participate, as required. Guidelines for authorship as guided by the International Committee of Medical Journal Editors http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html;

Rapid review process

Rapid review is a focused synthesis of the available evidence and is an appropriate tool during a pandemic (such as the Covid-19 pandemic) where time-sensitive questions of healthcare decision-makers need to be answered as fast as possible. At the same time, sound scientific rigor and methodology should be applied at all times.

Process

New questions may arise from:

- NDoH Executive Management
- Clinical Guideline Writing Committee on Covid-19
- Feedback from MAC or Vaccine MAC
- Feedback from Provincial Pharmaceutical Therapeutics Committees as a result of input from clinicians and patients.
- Feedback from NDoH
- Feedback from webinars on COVID-19 rapid reviews
- Horizon scanning of published evidence for COVID-19 therapeutics

Question prioritisation

The Committee may apply criteria to prioritise questions for a rapid review. Questions should meet the following criteria:

- Question is high priority to clinicians, patients and policymakers
- There is limited evidence and therefore uncertainty about the benefit or harm of the intervention
- There is research evidence emerging on the topic that may inform a recommendation

Conducting rapid reviews

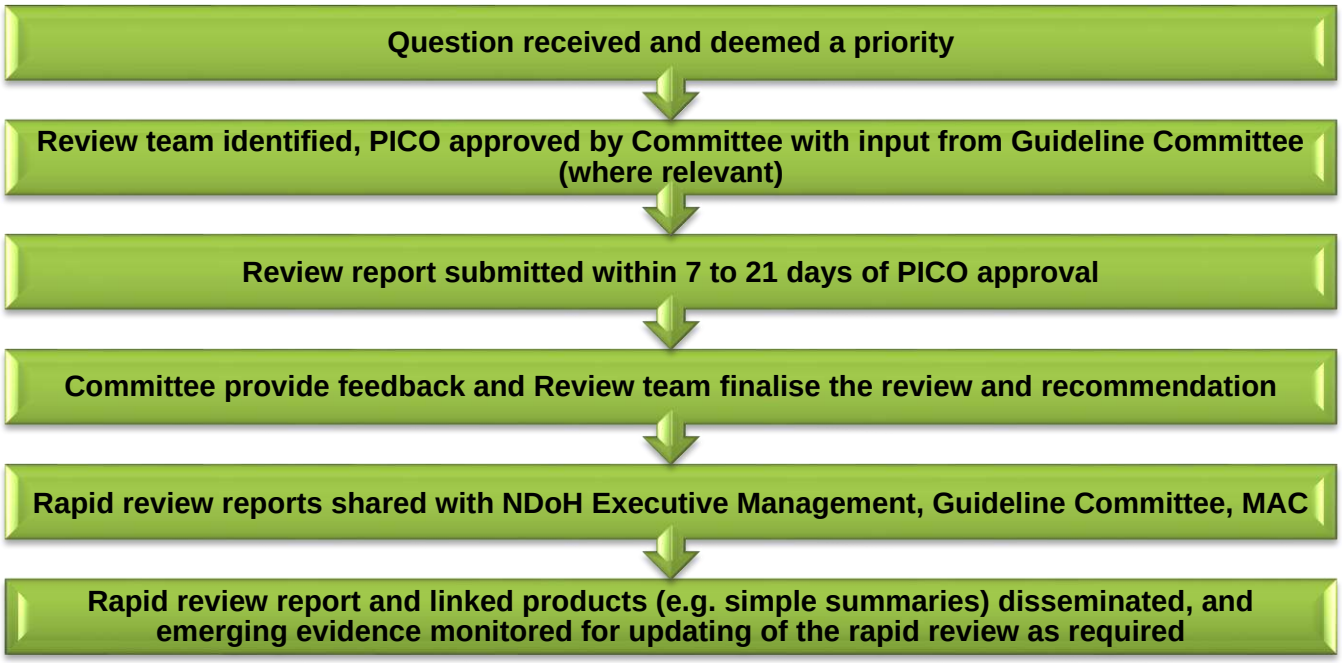
- A standard protocol including an outline of the Population, Intervention/s, Control, and Outcomes (PICO) and related methods will guide the conduct of rapid reviews.
- Review teams: A lead reviewer from the Committee, or delegated lead, oversees the process, drafts the PICO for approval ,and leads drafting of the background, key findings and recommendations. Two independent reviewers with experience of conducting evidence syntheses can be co-opted to support the review process. All co-opted reviewers must sign the conflict of interest and confidentiality forms.
- The PICO for each review is approved by the Committee in collaboration with the Clinical Guideline Committee, as required (Appendix 1: Generic PICO template).
- Rapid reviews evaluating the effectiveness of an intervention aim to summarise available systematic reviews, but where these are not available, randomised trials may be presented in the narrative format. In their absence observational studies may be reported.
- Rapid review reports (guided by a generic rapid review report template) should be submitted to the Committee within 7 to 21 days from the time of PICO approval (Appendix 2).
- The initial draft review is peer-reviewed by the Committee and a recommendation is prepared.
- Once the Committee has approved a rapid review report, the Secretariat finalises the report for public dissemination.
- All finalised reviews will be shared with the Executive Management of NDoH, the Clinical Guideline Writing Committee, MAC and IMT by the co-leads or NDoH Secretariat.
- Where recommendations differ from those in place in the current version of the COVID-19 National Guidelines, discussion and collaboration should take place to understand value aspects of decision-making between the Committee and the Clinical Guideline Writing Committee. Such liaison may be led by members of the Committee designated by the chairperson of the Committee.
- All reviews will be placed in an open access repository: http://www.health.gov.za/covid-19-rapid-reviews/
- Where relevant, rapid reviews will be adapted for information and use by different stakeholders including the public, and may be disseminated via relevant platforms including social media (e.g. development of a simple one page summary – see Appendix 3).

Updating reviews

As evidence is continuously emerging, the rapid reviews will be updated if and when more evidence becomes

available. However, to minimise duplication of efforts and facilitate efficient use of resources, completed systematic reviews and Health Technology Assessments (HTAs) identified in the literature may be reported in a rapid review with appropriate appraisal. Living systematic reviews will also be reviewed, and if used, acknowledged accordingly. Framework for updating rapid reviews is described in Appendix 4.

Figure 1: Steps in conducting a rapid review:



National COVID-19 Guidelines: Therapeutics module

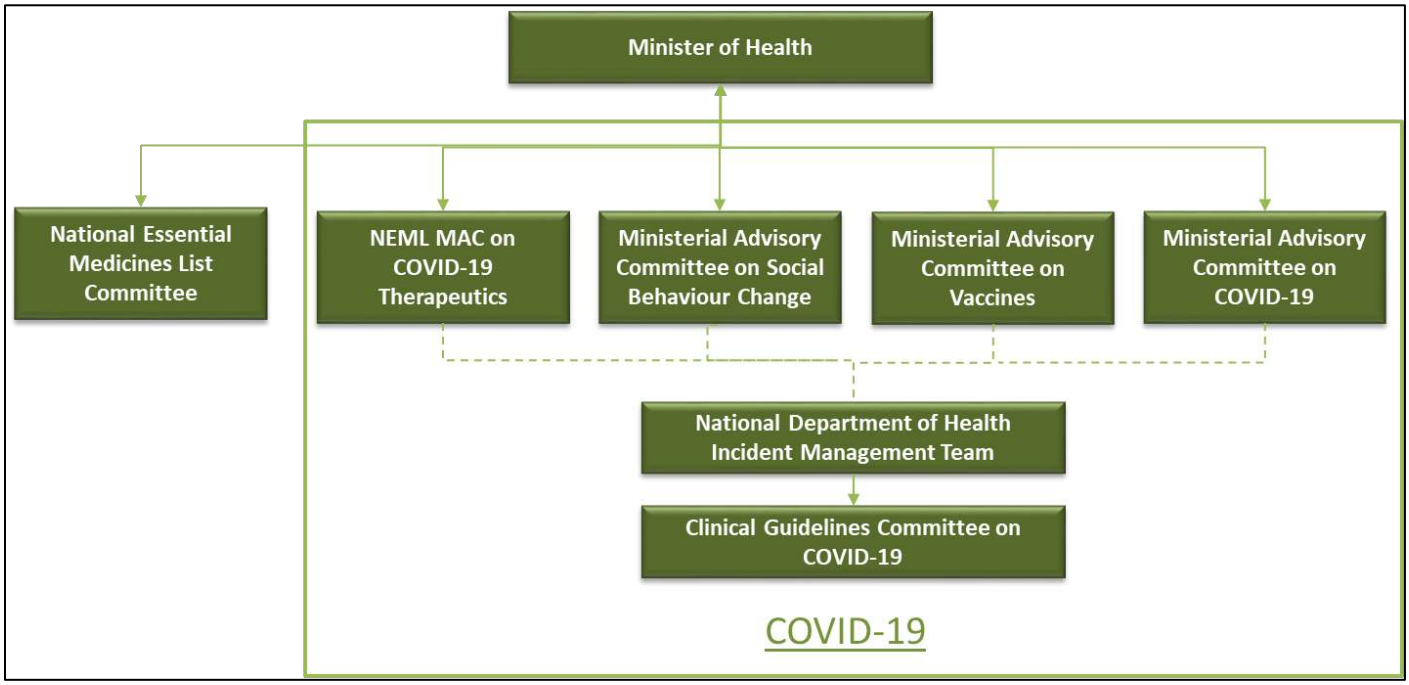
To ensure governance and alignment between NEMLC COVID-19 therapeutic rapid review recommendations and the National COVID-19 Guideline, Therapeutics module, updates of this module to be submitted to the NEMLC on COVID-19 Therapeutics for ratification, prior to publication.

Communication

The Chairperson of the NEMLC on COVID-19 Therapeutics, or nominated lead and co-lead will communicate the recommendations of the Committee to the Chairperson of the Clinical Guideline Writing Committee and the Lead of the Clinical Care work stream of the IMT, either directly or through the Secretariat supporting the Committee. The lead or co-lead may be invited as an observer, on request of the Chairperson of the Clinical Guideline Writing Committee or Chairperson of the MAC on COVID-19 or the Vaccine MAC, to participate in meetings of the Ministerial Advisory Committees (MAC) on COVID-19 as depicted below in Figure 2. This should be done in consultation with the lead of the Clinical Care work stream of the IMT.

The Secretariat will provide feedback on recent NEMLC COVID-19 therapeutic rapid review recommendations to the IMT, as required; and the Chairperson of the NEMLC on COVID-19 Therapeutics or nominated Committee member will present the respective evidence to IMT as required.

Figure 2: Communication between the Committees on Covid-19



Roles and Responsibilities

Stakeholder	Role and Responsibility
Clinical Guideline Writing Committee	• Review and updating of the Clinical Management Guideline for Covid-19. • Addressing of queries from stakeholders on the guideline.
Chairperson of the Clinical Guideline Committee	• Co-ordination of the development and updating of the guideline • Responds to queries from stakeholders on the guideline on behalf of the Committee • Communication of recommendations to the Clinical Care Lead of the IMT
Lead or Co-Lead of the NEMLC on COVID-19 Therapeutics	• Nominated by the Chairperson to communicate the NEMLC on COVID-19 Therapeutics recommendations to the Clinical Guideline Writing Committee on appropriate therapeutic management and/or share the recommendations of the Committee with the Executive Management of NDoH, MAC on Covid-19 and/or Vaccine MAC, either directly or through the Secretariat supporting the Committee.

Stakeholder	Role and Responsibility
Secretariat of the NEMLC on COVID-19 Therapeutics	• Develop and maintain a dynamic list of therapeutic agents to be prioritised for rapid review, as per Committee recommendations. • Convene meetings and make all the necessary logistic arrangements; or maintain electronic discussion within the Committee. • Facilitate the proper functioning of the Committee in accordance with the principles of good governance. • Compile minutes of meetings and finalise the draft in consultation with the Chairperson/ Vice-chairperson of the Committee. • Support the Committee pertaining to any research that is required and contribute to the development of rapid reviews as required. • Support with editing, formatting and publication of the final rapid reviews (on the required platform). • In consultation with the Chairperson/ Vice-chairperson of the Committee, source reviewers from NEMLC, Expert Review Committees or other organisations. • Maintain a list of relevant randomised controlled trials that have been completed and advise the Committee accordingly. • Provide feedback on recently NEMLC COVID-19 therapeutics rapid reviews to the IMT.
Director-General	• Approval of guideline.
Clinical Care Work stream of the IMT	• Clinical editing of guideline. • Formatting of guideline. • Dissemination of guideline to the Communications Department of NDoH. • Receipt and coordination of queries from stakeholders on the guideline and communication thereof to the Chairperson of the Clinical Guideline Writing Committee.
Lead of the Clinical Care Work stream of the IMT	• Addressing queries from stakeholders on the guideline.
Communications Department	• Dissemination of the guideline to all internal and external stakeholders.

Version	Date	Revisions
1.1	11 May 2020	N/A; Initial version
2.0	4 June 2020	Appendix 1 – Population 1 amended from “pre-hospital” to “ambulatory” Appendix 2 – Evidence to decision framework added to rapid review report
3.0	25 July 2020	Appendix 2 – Summary of findings table added; Evidence to decision framework updated
4.0	26 November 2020	Appendix 1 – Included clinical improvement on an ordinal scale that may be considered as an outcome. Appendix 4 – Framework for updating rapid reviews

		Appendix 2 – updated to include rationale for updating a review
5.0	9 March 2021	Period for completion of review amended from “1 week” to “7 to 21 days” from approval of the PICO.
6.0	15 September 2021	NEMLC Therapeutic Guidelines Subcommittee on COVID-19 reconstituted to ministerial appointed NEMLC on COVID-19 Therapeutics. Reporting process updated - COVID-19 therapeutic recommendations reported directly to the NDoH Executive Management. Responsibilities relating to publishing of rapid reviews and rapid review process. Appendix 1 – PICOs updated, as evidence is starting to mature Appendix 2 – Evidence to decision framework updated

APPENDIX 1: Generic PICO for COVID-19 rapid reviews

Process – preliminary overview of the agent to determine if it is being used in multiple severity stages or only one. If the latter, only use PICO for that stage; if the former either do separate reviews per stage, or if a single review is planned (likely until evidence base much larger) then ensure that subgroup analyses focus on endpoints appropriate for each level of severity being considered.

Population 1 – ambulatory Ambulant patients with confirmed COVID-19, no restriction to age but disease sufficiently mild that management outside hospital is feasible.
Intervention Medicine under review either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.
Comparators Any (standard of care/placebo).
Outcomes Mortality; progression to hospitalisation; proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis; time to negative SARS-CoV2 PCR on nasopharyngeal swab; adverse reactions and adverse events.

Population 2 – hospitalised Patients with confirmed COVID-19, no restriction to age but disease severity such that hospitalisation required.
Intervention Medicine under review either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.
Comparators Any (standard of care/placebo).
Outcomes Mortality; duration of hospitalisation; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay; duration of mechanical ventilation; adverse reactions and adverse events.

Population 3a – requiring oxygen Patients with confirmed COVID-19, no restriction to age but severe disease requiring oxygen or ventilatory assistance.
Intervention Medicine under review either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.
Comparators Any (standard of care/placebo).
Outcomes Mortality; progression to mechanical ventilation; duration of ventilatory support; duration of mechanical ventilation; duration of ICU stay; adverse reactions and adverse events.

Population 3b – requiring ventilatory support (non-invasive/invasive) Patients with confirmed COVID-19, no restriction to age but severe disease requiring oxygen or ventilatory assistance.
Intervention Medicine under review either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.
Comparators Any (standard of care/placebo).
Outcomes Mortality; duration of ventilatory support; duration of mechanical ventilation; duration of ICU stay; adverse reactions and adverse events.

Population 4 – prophylaxis Patients at risk of COVID-19 but currently asymptomatic, no restriction to age or comorbidities
Intervention Medicine under review either alone or in combination with other medicines. No restriction on dose or frequency.
Comparators Any (standard of care/placebo).
Outcomes Development of COVID-19 with positive SARS-CoV-2 PCR; duration of symptoms; proportion requiring hospitalisation; adverse reactions and adverse events.

Various scales are used to measure outcomes in COVID-19 clinical trials and the World Health Organisation R&D Blueprint expert group has proposed the following:

ORDINAL SCALE FOR CLINICAL IMPROVEMENT SCORE		
Patient state	**Descriptor**	**Score**
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalised: mild disease	Hospitalised, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalised: severe disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Reference: World Health Organisation R&D Blueprint for the novel Coronavirus, Covid-19 therapeutic trial synopsis, February 18, 2020. https://www.who.int/teams/blueprint/covid-19

Note: Clinical improvement on an ordinal scale at chosen time points may be considered as an outcome.

APPENDIX 2

South African National Department of Health
Rapid Review Report
Component: COVID-19

TITLE:

Date:

Key findings

- *x*
- *x*
- *x*

NEMLC ON COVID-19 THERAPEUTICS RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	
Rationale: **Level of Evidence:**					

(Refer to appendix 2 for the evidence to decision framework)

APPENDIX 2

BACKGROUND

RESEARCH QUESTION: Should *therapeutic agent* be used for managing COVID-19?

METHODS

Eligibility criteria for review

Population:

Intervention:

Comparators:

Outcomes:

Study designs:

RESULTS

CONCLUSION

Reviewers:

Declaration of interests:

REFERENCES

APPENDIX 2

Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Main findings

Table 2. Characteristics of planned and ongoing studies

Citation	Study design	Population (n)	Treatment

Table 3: Summary of findings

Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with *Intervention*	Risk difference with *Intervention*			
	x per 1.000	**y per 1.000** (95% CI)	z fewer/more per 1.000 (95% CI)	**RR (95% CI)**		

Appendix 1: Search strategy

Database A *Search strategy* *Output*
Database B *Search strategy* *Output*

Appendix 2: Evidence to decision framework

Desirable Effects		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Trivial o Small o Moderate o Large o Varies o Don't know		

Undesirable Effects		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Large o Moderate o Small o Trivial o Varies o Don't know		

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Very low o Low o Moderate o High o No included studies		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Important uncertainty or variability o Possibly important uncertainty or variability o Probably no important uncertainty or variability o No important uncertainty or variability		

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know	*• Judgments regarding each of the four preceding criteria* *• To what extent do the following considerations influence the balance between the desirable and undesirable effects:* *- How much less people value outcomes that are in the future compared to outcomes that occur now (their discount rates)* *- Risk averse attitudes* *- Risk- seeking attitudes*	

Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	*• How large is the difference in each item of resource use for which more resources are required?* *• Have all-important items of resource use that may differ between the options being considered been identified?*	

APPENDIX 2

Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o No included studies	*• Judgments regarding each of the six preceding criteria* *• Is the cost-effectiveness ratio sensitive to one-way sensitivity analyses?* *• Is the cost-effectiveness ratio sensitive to multi-variable sensitivity analyses?* *• Is the economic evaluation on which the cost-effectiveness estimate is based reliable?* *• Is the economic evaluation on which the cost-effectiveness estimate is based applicable to the setting(s) of interest?*	
Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Reduced o Probably reduced o Probably no impact o Probably increased o Increased o Varies o Don't know	*• Are there groups or settings that might be disadvantaged in relation to the problem or options that are considered?* *• Are there plausible reasons for anticipating differences in the relative effectiveness of the option for disadvantaged groups or settings?* *• Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention or the importance of the problem for disadvantaged groups or settings?* *• Are there important considerations that should be made when implementing the intervention in order to ensure that inequities are reduced, if possible, and that they are not increased?*	
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o No o Probably no o Probably yes o Yes o Varies o Don't know	*• Are there key stakeholders that would not accept the distribution of the benefits, harms and costs?* *• Are there key stakeholders that would not accept the costs or undesirable effects in the short term for desirable effects (benefits) in the future?* *• Are there key stakeholders that would not agree with the values attached to the desirable or undesirable effects (because of how they might be affected personally or because of their perceptions of the relative importance of the effects for others)?* *• Would the intervention adversely affect people's autonomy?* *• Are there key stakeholders that would disapprove of the intervention morally, for reasons other than its effects on people's autonomy (e.g. other than its effects on people's autonomy (e.g. in relation to ethical principles such as no maleficence, beneficence or justice)?*	
Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o No o Probably no o Probably yes o Yes o Varies o Don't know	*• Is the intervention or option sustainable?* *• Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it?*	

APPENDIX 2

Subgroup considerations

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Implementation considerations

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Monitoring and evaluation

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Research priorities

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Appendix 3: Updating of a rapid report

Date	Signal	Rationale

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale

For internal NDoH use:
WHO INN:
ATC:
ICD10:

APPENDIX 3: SUMMARY TEMPLATE

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

Rapid Review for COVID-19

Simplified question reviewed

e.g. "Should chloroquine be used to treat COVID-19?"

one sentence in bold

Introduction to the medicine in question, including what it is currently used for and background to the review

3-5 sentences

Summary of evidence reviewed, including number of trials, number of participants, publication dates and key findings

3-5 sentences

Summary of conclusion, including strength of evidence and the evidence for and against the question to be answered

3-5 sentences

Final answer to the question

e.g. "Chloroquine is not recommended to treat chloroquine outside of a clinical trial setting."

one sentence in bold

Date of publication and link to the date-stamped rapid review

e.g. "Date of Publication: 5 May 2020. See the full medicine review at http://www.health.gov.za/covid-19-rapid-reviews/

Note: As evidence is continuously emerging, the rapid review will be updated if and when more relevant evidence becomes available.

APPENDIX 4: FRAMEWORK FOR UPDATING A REVIEW

Initially, the need for revision of rapid reviews was decided on an *ad hoc* basis. As the body of evidence expands, an explicit framework informing update decisions for rapid reviews is required. Existing reviews contain an explicit evidence to decision framework and recommendation. Sensible stewardship of reviewers' time requires screening of new information to gauge the probability that it will lead to a change in a recommendation. This necessarily happens before a full GRADE-level review of the new evidence; once that has happened, the resources/time has already been expended. This framework aims to guide recommendations for review updating and provide a governance record of these decisions.

Considerations favouring the updating of a review:

1. Emerging evidence of efficacy that appears likely to impact the recommendation.
2. A new signal of harm likely to impact a recommendation.
3. Important change in cost-effectiveness estimates, either from new prices or a change in the health service delivery environment.
4. Generally, where the recommendation is weak or in equipoise, have a lower threshold to consider new evidence.

Factors unlikely to prompt an update:

1. New high-quality efficacy evidence pointing in the same direction as previous evidence where an existing recommendation is already strong, unless providing new clinically useful details of value to guideline development.
2. New evidence of efficacy that appears of lower quality than that already reviewed.
3. New evidence of harm when the review already contains a strong recommendation against use.
4. Cost-effectiveness analyses where a review has failed to find clinically meaningful evidence of efficacy.

Signals not to be used on their own for updating a review:

1. Press releases
2. Approval by Regulatory Authorities for emergency use authorisations (EUA)

When to retire a review:

1. High certainty data
2. Existing strong recommendation
3. Evidence that 'zone of futility' has been reached (where there is high probability that further evidence accrual is unlikely to change a meta-analytic conclusion.)

Process:

1. When a new signal is detected, the secretariat to inform both the authors of the original review and the Committee.
2. The authors to indicate whether they think the new information warrants a review update based on the guiding principles listed above.
3. A decision to be made through email correspondence amongst committee members, with the framework-based reason for the proposed decision explicitly stated.
4. If the decision is unanimous then it is date-stamped and recorded as such, with the signal and the reason for the decision placed as an addendum to the review (see the rapid review report template, Appendix II: of the Terms of Reference).
5. If there is not unanimity or rapid resolution by email or verbal communication, then the updating decision is to be brought to the next NEMLC on COVID-19 Therapeutics meeting for discussion and resolution.

Algorithm to guide decision-making