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Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

National Essential Medicines List (NEML) Ministerial Advisory Committee (MAC) on COVID-19 Therapeutics Terms Of Reference

12 MARCH VERSION 7.0

Contents

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
WHO	-	World Health Organization

Introduction

Outbreaks of emerging and re-emerging infectious diseases present 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, and the lessons that can be learnt for a future pandemic.

Purpose and Scope

The National Essential Medicines List (NEML) Ministerial Advisory Committee (MAC) on COVID-19 Therapeutics replaces the previous NEMLC COVID-19 Subcommittee and is now constituted as a separate ministerially-appointed advisory committee (from 24 August 2021). This MAC is tasked with providing specific patient-focused evidence-based recommendations to support the inclusion of selected medicines in the National Department of Health (NDoH) *Clinical Management of Suspected or Confirmed Covid-19 Disease Guideline*. This guideline applies to situations where existing guidance from standard treatment guidelines (STGs) of similar clinical conditions (e.g. pneumonia, severe acute respiratory distress) is lacking. The guidelines are therefore to be used in addition to the current NEMLC-approved Standard 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 the NEMLC. However, the medicines recommended will not automatically be added to the EML and the therapeutic recommendations will apply only during the current pandemic, but will be reviewed by the NEMLC once the state of disaster has been lifted. Given the need for rapid recommendations which are frequently updated, the usual stakeholder engagement and appeals processes employed by the NEMLC will not apply to the NEML MAC on COVID-19 Therapeutics.

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;
- 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 pandemic.

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 NEML MAC on COVID-19 Therapeutics will be dissolved once the Clinical Guideline Writing Committee on COVID-19 is dissolved.

Membership

The NEML MAC on COVID-19 Therapeutics comprises current or previous members of the ministerially- appointed NEMLC, members of the ministerially-appointed Expert Review Committees, and additional members appointed by the Minister of Health, including persons with expertise in evidence-based medicine and medicines regulatory practice). 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.

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 (see Annexure I and II).

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) will apply.

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 quickly as possible. At the same time, sound scientific rigour 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 the MAC on COVID-19 or the Vaccine MAC
- Feedback from Provincial Pharmaceutical Therapeutics Committees as a result of input from clinicians and patients.

- Feedback from NDoH programmes
- 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

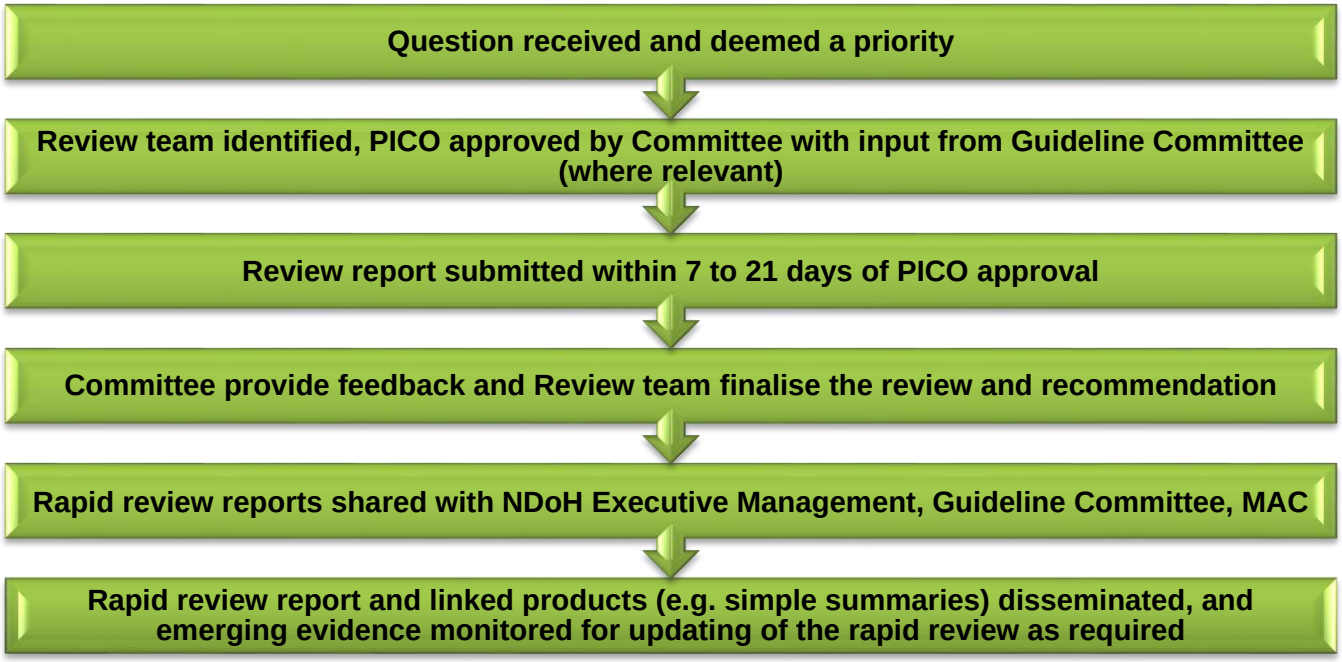
- A standard protocol including an outline of the Population, Intervention/s, Control, and Outcomes (PICO) and related methods will guide the conduct of rapid reviews.
- Review teams: A lead reviewer from the Committee, or delegated lead, will oversee the process, draft the PICO for approval and lead drafting of the background, key findings and recommendations. Up to two independent reviewers with experience of conducting evidence syntheses may be co-opted to support the review process. All co-opted reviewers/methodologists will need to sign the conflict of interest and confidentiality forms.
- The PICO for each review will be 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 relied upon.
- Rapid review reports (guided by a generic rapid review report template) shall be submitted to the Committee within 7 to 21 days from the time of PICO approval (Appendix 2).
- The initial draft review will be peer-reviewed by the Committee and a recommendation prepared.
- Once the Committee has approved a rapid review report, the Secretariat will finalise the report for public dissemination.
- All finalised reviews will be shared with the Executive Management of NDoH, the Clinical Guideline Writing Committee, MAC on COVID-19, Vaccine 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 shall take place between the Committee and the Clinical Guideline Writing Committee, in order to understand the basis for the recommendation. Such engagement 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. The framework for updating rapid reviews is described in Appendix 4.

Figure 1: Steps in conducting a rapid review:



National COVID-19 Guidelines: Therapeutics module

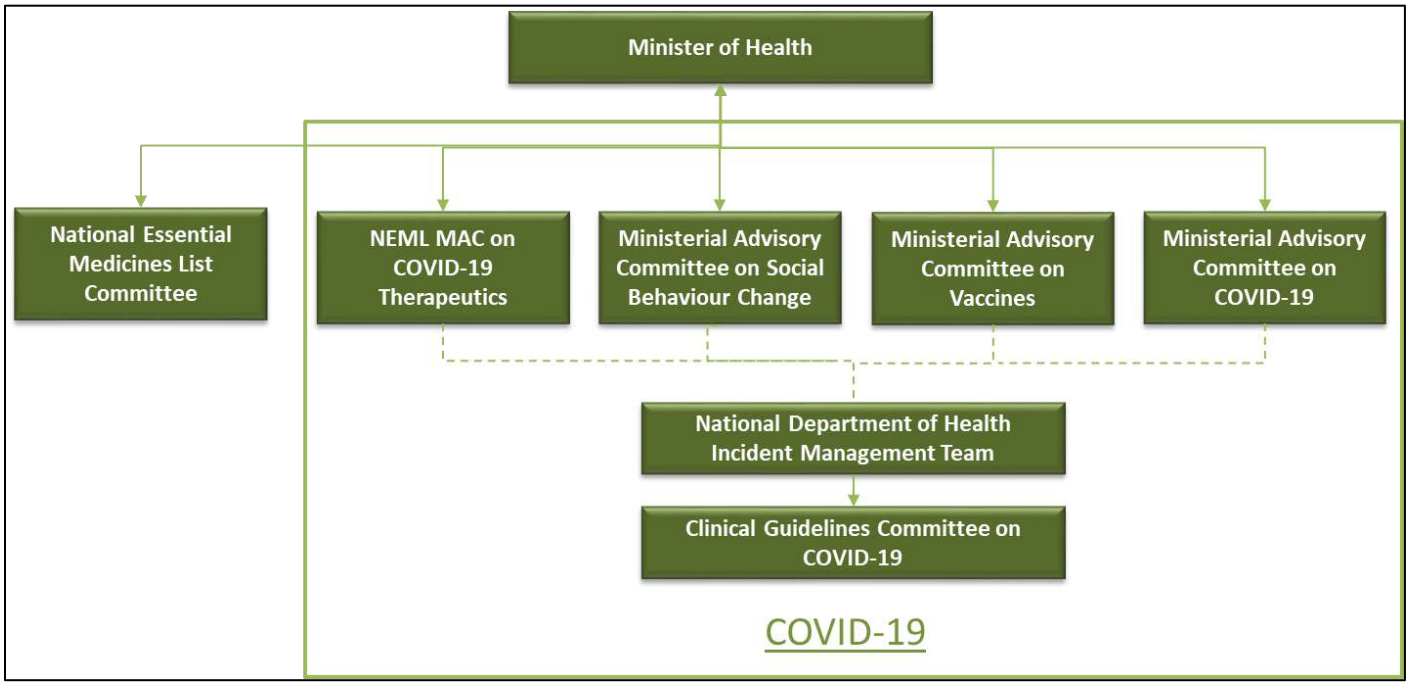
To ensure governance and alignment between NEML MAC on COVID-19 Therapeutics rapid review recommendations and the National COVID-19 Guideline, updates of the Therapeutics module will be submitted to the NEML MAC on COVID-19 Therapeutics for input, prior to publication.

Communication

The Chairperson of the NEML MAC 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 NEML MAC on COVID-19 Therapeutics rapid review recommendations to the IMT, as required; and the Chairperson of the NEML MAC 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



Interaction with external parties

Requests for engagement with any external party shall be referred to the National Department of Health and/or Minister of Health, who may request further advice, where needed.

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 • Response 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 NEML MAC on COVID-19 Therapeutics	• Nominated by the Chairperson to communicate the NEML MAC 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.
Secretariat of the NEML MAC 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 draft reviews in consultation with the Chairperson/ Vice-chairperson of the Committee. • Support the Committee with respect 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 NEML MAC on COVID-19 Therapeutics rapid reviews to the IMT.
Director-General	• Approval of guideline.

Stakeholder	Role and Responsibility
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
7.0	12 March 2022	Differentiation between NEML MAC on COVID-19 therapeutics versus NEMLC processes. Interaction with external parties added. NEMLC conflict of interest policy and declaration of policy attached as annexures Appendix 2 – Key findings updated, PROSPERO registration number added

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NATIONAL ESSENTIAL MEDICINES LIST COMMITTEE (NEMLC)

Confidentiality Guidance Document

A code of practice for the National Essential Medicines List Committee and members of the technical expert review committees

Background

Confidentiality and transparency are not mutually exclusive and a balance needs to be struck between managing risk whilst maintaining the appropriate degree of transparency required for sound technical decision-making and protection of constitutional rights.

A risk is any event that affects the performance and viability of the review program and/or its external stakeholders. In terms of leaked information the risk broadly translates into:

- loss of credibility
- decisions are made externally based on draft material
- reluctance of members to participate in the process and/or loss of momentum of the review
- negative impacts upon the procurement process of the government
- negative business consequences for various parties including suppliers

In addition to the product of the review which is within the public domain any member of the public may utilise the avenue of the Promotion of Access to Information Act ("PAIA"), provided such requests are reasonable and have been made in compliance with the administrative procedures that makes provisions for such access.

1. Introduction

This code of practice guides the National Essential Medicines List Committee (NEMLC) members, members of the expert review committees and any working groups that the committee may, from time to time, establish as to the circumstances in which they should maintain confidentiality regarding the decisions of the committee and its source documents.

2. Scope and definitions

2.1 Scope

This code applies to:

- The Chairperson and NEMLC members.
- Members of expert review committees appointed by the Minister. This also includes co-opted members and members of any working groups that the NEMLC may, from time to time, establish.

2.2 Definitions

In this Code:

- "Pharmaceutical industry" means companies, partnerships or individuals who are involved with the manufacture, sale or supply of medicines as defined in the Medicines and Related Substances Act (Act 101 of 1965) that are, or may be, used by state institutions, as well as trade associations representing companies involved with such products.
- "Professional organisations" refers to colleges, health professional associations and societies, and universities.
- "Members" includes the NEMLC and all its expert review committees.
- "Administrative unit" is a department or organisation with which the member has an employment relationship with managerial responsibilities.
- "Employees" refers to full and part time employees of the NDoH.
- "Confidential business information" commercial or financial information considered to be confidential because disclosure may:
  - Impair the Government's ability to obtain necessary information in the future; or
  - Cause substantial harm to the competitive position of the individual or business entity which provides the information.
- "Proprietary information" is information or data belonging to an owner or proprietor, who may have exclusive rights to the manufacture and sale of a specific item.
- "Trade secret" is any formula, pattern, device, or information that is used in business which provides a competitive advantage.
- "Sensitive information" Information or data in which disclosure, loss, misuse, alteration, or destruction may adversely affect national security or other government interest.
- "Promotion of Access of Information Act" or "PAIA" Section 32(1)(a) of the Constitution of the Republic of South Africa Act, No. 108 of 1996 provides that everyone has a right of access to any information held by the state and any information held by another person that is required for the exercise or protection of any rights. The Promotion of Access to Information Act, No. 2 of 2000 is the national legislation which was enacted to give effect to the constitutional right of access to information.
- "Internal stakeholders" are those subcommittees or task teams constituted by the NEMLC with established terms of reference.
- "External stakeholders" refers to all stakeholders that have not been designated as internal or who have been granted access to the documentation in terms of a resolution of the NEMLC.

3. Types of information that are considered confidential

The following is intended as a guide to the types of information and situations which should remain confidential. Where a member or employee is uncertain as to whether information should be disclosed to an external party he or she should seek guidance from the chairperson of the NEMLC, or National Department of Health secretariat. Alternatively, the interested party should be referred to the National Department of Health's information officer appointed in terms of PAIA and the relevant manual published by this officer. Further guidance as to implementation of PAIA such as grounds for refusal can be found at http://www.doj.gov.za/paia/paia.htm.

Different types of confidential information can be envisaged and the following list, which is not exhaustive, is provided as guidance.

- Identity of a reviewer of a specific chapter, the review of the EML follows a process of consensus seeking around evidence based principles and hence the decision of the committee is that of a collective and not an individual. Disclosure of an individual's identity poses certain risks which include;
  - Exposure of the review processes to potential undue pressures from external stakeholders and parties with vested interests which may:

        - Discredit the objectivity and impartiality of the review process.
        - Introduce conflict of interests as contemplated in the relevant policy on this matter.
    - In addition, disclosure of the individual's identity may negatively impact upon that reviewer's willingness to participate in future reviews.
- Although the EML process does not routinely utilise information that may be considered propriety any such information that is supplied to the committee should enjoy the protection of the appropriate level of confidentiality.
- Leaked information poses a specific list of risks as it may, for example:
    - Prolong the review process through the introduction of subjective information by individuals with a vested interest prior to the finalisation of the evidence based consensus process.
    - Provide a competitor a business advantage to a potential supplier in which case it would be considered a trade secret.
    - Have a negative impact upon the Department of Health's ability to generate competition and hence obtain the best price for a pharmaceutical commodity and it would therefore be considered confidential business information.
    - Have a negative impact upon the government actualising a public health outcome in which case this information would be deemed sensitive information.
    - Be implemented as policy prior to finalisation of the consensus seeking process.

Leaked information is any information that an individual has access to which is not in the public domain. This includes all documents that are actively being reviewed by NEMLC or its Expert Review Committees, unless approved for external consultation as contemplated in the terms of reference. In its resolution of acceptance of a technical document the NEMLC should declare the level of confidentiality and for documents approved for consultations and the scope of the consultation.

4. Position of the chairperson

The Chairperson of the NEMLC is the individual responsible for compiling information to be communicated to the information officer for disclosure in terms of any approved PAIA application. The NEMLC chairperson may consult with the secretariat or the chairman of the relevant Expert Review Committees in the compilation of such documentation. The affected committee should be informed of such disclosure and should be furnished with a copy for their reference. The nature, but not necessarily the details of communication with internal and external stakeholders, should be declared as part of the proceedings of the affected committee. In meetings with stakeholders on technical matters the relevant chairperson of the technical committee will act as the spokesperson supported by any member of the committee who has agreed to such a meeting and members of the secretariat. The secretariat may meet with stakeholders to discuss matters that are of a procedural or administrative nature or to clarify a technical matter which requires expertise available in the secretariat provided that the member of the secretariat has been present in the relevant deliberations.

5. Maintenance of confidentiality

Committee members should be provided with a copy of the confidentiality policy and upon review must sign a confidentiality agreement:

- on appointment, and
- annually

using the format provided in **appendix A**

The committee secretariat will provide the member with the policy and ensure that the confidentiality agreement has been received upon appointment and then annually.

All source documentation must comply with relevant copyright provisions and should remain confidential unless approved by the NEMLC. During the review strict confidentiality must be maintained on all draft documents until consensus have been reached at the level of the NEMLC that such a document may be released for consultation or public consumption. Members of the technical committee must note that consensus and approval by the sub committee does not lift the confidentiality restriction until such time as the NEMLC has pronounced on the matter. A reviewer may however consult with experts in accordance with the terms of references and in consultation with the relevant committee. Where such consultation requires the disclosure of any significant sections of technical documents the recipient must sign a confidentiality agreement using the format provided in **appendix A.** When the restriction is lifted the expert should be informed of such.

For the purposes of confidentiality the restriction refers to information contained in the document whether it is disclosed verbally, electronically or as a hard copy.

The maintenance of confidentiality also requires procedural safeguards. Final minutes tabled at the NEMLC should not identify the names of individuals although the working version may have transient reference to individuals using initials in order to track contributions that are outstanding. Although the minutes adopted by the technical committee may have residual reference to these initials their removal is considered mandatory and administrative.

All materials related to the review process must be stored in a secure manner to prevent unauthorised access. They must be transmitted using secure carriers and technologies. When documentation is no longer required, it must be destroyed using a secure method such as burning or shredding or returned to the secretariat for destruction.

When a member is faced with a request for information by an external stakeholder which he or she feels has merit or is in the interest of public health they should consult the chairperson of the relevant Expert Review committee who in turn will refer the matter to the chairperson of the NEMLC unless the aforementioned has delegated such powers.

A copy of the confidentiality policy should be available to any member of the public who expresses an interest in accessing information or where they are of the opinion that the agreement has been transgressed.

6. Handling of disclosure of confidential information

A determination should be made as whether the disclosure was:

- outside of the provisions of this policy, or
- inadvertent, or
- clearly in disregard of this policy.

Furthermore discussion should be lead with respect to the harm or potential harm such a disclosure may have held for the review process, individuals who have contributed or the government.

The chair in consultation with the committee may rule that:

- The member reviews the policy and discusses its provisions with the chairperson and signs a new confidentiality agreement.
- The member takes corrective measures in order to prevent further inadvertent disclosures.
- The member is excluded from participation of meetings and/or consultation.

7. Record of agreement

The secretariat should keep a record of:

- names of individuals who signed agreements on appointment, as the need first arises or through the annual process.
- names of individuals who have declared interests at meetings giving dates, names of relevant products and companies, details of the interest declared and whether the member took part in the proceedings.

8. Publication

Information regarding this policy and agreements with members may be made available to third parties if compelled in terms of the Rules of Court pursuant to litigation or by virtue of the provisions of the Promotion of Access to Information Act, 2000 (Act 2 of 2000). The latter requires the protection of personal information and contains procedures which require consultation with the person to whom the information relates. Therefore in the event of compulsory disclosure, this will not take place without prior consultation with the affected party.

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Affordable Medicines Directorate

Conflict of Interest Policy

Version 1

1. Introduction

This policy outlines the principles and process of identifying and managing actual, potential or perceived conflict of interest of individuals involved in any committee operating under the auspices of the Affordable Medicines Directorate (AMD) of the National Department of Health (NDoH).

It deals with the identification, declaration, assessment and management of any interest/s of an individual, which may conflict with the duties and/or decision making of a committee, such that the individual concerned may not be independent, objective and impartial in relation to such duties.

Decisions taken by committees could have a substantial impact on the health and well-being of South Africans as well on the spending of public funds. There may also be direct or indirect consequences of these decisions which may include, but are not limited to, changes in clinical practice, utilisation and uptake of medicines, systems and/or technologies, supply chain considerations, integrity of master data and perceived validation of prior research.

The interests of all individuals who could influence the decisions or duties of a committee must be identified, declared, assessed and managed, to as far as possible, prevent any advice or recommendation made by a committee being challenged on the basis of an actual or perceived conflict of interest of individuals involved. The personal interests of any member or other meeting participant, should not take precedence over the interests of public health.

Appropriate management of actual, potential or perceived conflict of interest protects the reputation and integrity of committees by helping to ensure their impartiality and independence. This helps to ensure that the advice and recommendations provided reflect the highest standards of professionalism and minimise risk to the NDoH.

Implementation and adherence to this policy will assist in confirming that the work done by committees is transparent, and that decisions taken are balanced, credible, independent of bias, and of a high ethical standard.

2. Abbreviations and Definitions

2.1. Abbreviations

AMD	Affordable Medicines Directorate
COI	Conflict of Interest
DOI	Declaration of Interest
NDoH	National Department of Health

2.2. Definitions

Assessor of interest means the person who is responsible for the assessment of the conflict of interest or potential conflict of interest of an individual.

Chairperson means the person elected, appointed or nominated in accordance with the terms of reference of the relevant committee.

Commercial entity means any commercial company, organisation, individual, group or association that has or may have a direct or indirect interest in the decisions and work undertaken by a committee, and includes legal or natural persons who (i) own a majority stake in, or otherwise exercise a significant influence in the decision-making processes of the relevant commercial entity; (ii) are controlled by; or (iii) are under common control of a commercial entity and includes non-profit entities, as well as researchers and research organisations such as universities.

Committee means any committee which operates under the auspices of the AMD.

Conflict of interest means any financial or other interest or undertaking that could directly or indirectly compromise the performance of an individual's duties in a committee, or the reputation of a department within the public service in its relationship with its stakeholders.[1]

Co-opted expert means an individual with particular expertise in a specific field who performs a technical review and/or provides input to a committee whether verbally or in writing, regardless of whether or not such input is provided in terms of a contract signed with such person.

Immediate family member means an individual within the close family circle or first degree relative of a natural person such as a sibling, parent, child, partner or spouse.

Interest means any direct or indirect investment or involvement in an undertaking.

Member means an individual appointed to a committee in accordance with the terms of reference of such committee.

Meeting participant means an individual temporarily included and/or co-opted, as well as observers or any other individuals attending any meeting of a committee.

Personnel means individuals employed by the NDoH.

Vice-Chairperson means the person elected, appointed or nominated in accordance with the terms of reference of the relevant committee.

3. Purpose of the policy

The purpose of this policy is to protect the integrity of decision-making of committees operating under the auspices of the AMD, through the identification, declaration, assessment, management and disclosure of any interest/s of individuals which relate to the work of committees. It provides for the management of actual and potential conflict of interest, and where appropriate, recusal or exclusion of individuals from involvement in discussions and/or decision making.

4. Scope of the policy

This policy applies to chairpersons, all committee members, other meeting participants as well as personnel involved in the management and technical activities of a committee and includes

[1] Section A(1) Notice 865 of 2009 The Public Service Commission Rules of the Public Service Commission: Managing Conflicts of Interest identified through the Financial Discloser Framework for Senior Managers

any other individual present at any meeting of a committee or involved in any way with the work of such committee.

5. Categorisation of Interests

When identifying and managing interests, it is important to determine both the nature and type of interest of an individual to enable effective, consistent and transparent management thereof.

Interests may be categorised as specific or non-specific. A **non-specific interest** is one where the actual or potential conflict relates to a general area of interest or involvement of an individual. A **specific interest** relates to a situation where the actual or potential conflict of interest of an individual relates directly to a matter under consideration by a committee.

The distinction between 'specific' and 'non-specific' interests determines the process and timing of addressing any actual, potential or perceived conflict of interest.

5.1. Types of interests

An interest may also be categorised based on whether or not an individual derives personal or non-personal benefit, and then categorised further based on whether or not he/she derives a financial benefit therefrom. (Refer Appendix 1)

5.1.1. Personal and non-personal interests

An interest is considered to be "personal" if the individual or an immediate family member of such individual gained, or currently gains, monetary or other value in their personal capacity from an interaction with any commercial entity that has or may have an interest in the activities of the committee. Personal interests include but are not limited to, financial gain, personal opinions, research interests or any other interests.

An interest is considered to be "non-personal" if an individual is employed by or contracted to an organisation or institution that gained, or currently gains monetary or other value from an interaction with any commercial entity, which has or may have an interest in the activities of the committee and decisions made by the committee.

5.1.2. Financial interests

Personal and non-personal interests can be divided further into financial or non-financial interests.

Financial interests include any arrangement or relationship where there is the opportunity for financial gain or benefit from a commercial entity by the individual or one of his/her immediate family members, or an organisation where the individual was employed, or to which he/she was contracted in at least the past four years or is expected to be employed or contracted in the next year. This period may be extended if the person declaring an interest believes that it is necessary to declare any interest or potential interest outside this period. This includes interests of a monetary or economic nature that are foreseen as possible or probable, including signed or anticipated contractual arrangements with commercial entities.

Personal financial interests include but are not limited to:

- Any employment, consultancy, directorship, or other position with a commercial entity which attracts regular or occasional payments in cash or kind, or an ongoing negotiation concerning prospective employment or other association with such commercial entity;
- Financial interests in a commercial entity by an individual or his/her immediate family member;
- Any payments for service or research made to an individual or his/her immediate family member in at least the past four years or expected to be made in the next one year, by a commercial entity;
- Any investments (include shares, equity or bonds) in a commercial entity held by the individual, where the individual has control over the selection of shares/composition of the fund, but excludes unit trusts and pension funds in which the individual has no control over the related investments;
- Intellectual property rights (e.g. patents, patents in which the individual has a financial interest, copyrights, and royalties from such rights);
- A financial interest in a substance, technology or process to be considered in, or otherwise related to, the subject-matter of the meeting or work of the committee;
- Any expenses or hospitality provided by a commercial entity; or
- Any research grants, travel imbursements or consulting arrangements sponsored by a commercial entity, other than the employer of the individual concerned, including the NDoH, a Provincial Department of Health or any other organisation.

Non-personal financial interests involve payments or other financial benefits made in the past to a department or organisation by which the individual is employed or to whom he/she is affiliated, but which is not received personally, e.g. commercial grants, sponsored fellowships, funds for a post, unit, consultancy services, travel or research.

5.1.3. Non-financial interests

Personal non-financial interests include but are not limited to:

- any clear opinions an individual may hold, or published statements in which he/she expressed a clear opinion on a matter under review as a result of a research project, evidence review, or association with a society, charity, advocacy group, academic institution or any other organisation related to the specific and non-specific areas of focus of the committee;
- any reputational risks to the individual in relation to the matter under consideration;
- personal areas of interest;
- representation on boards, research bodies, statutory bodies, committees or other bodies undertaking the development of other guidelines; or
- access to classified or proprietary information that the individual cannot disclose to the committee.

Non-personal non-financial interests refer to any published statements or official positions held by the organisation by which the individual is employed or to which he/she is contracted, or association, charity or advocacy group of which the individual is a member; where a clear opinion about the intervention under review has been expressed, which may be perceived to alter behavior and of which the person declaring an interest is aware.

6. Declaration of Interests

Each member or other meeting participant must identify and declare all interests prior to a meeting of a committee. When an individual is uncertain as to whether an interest should be declared, he or she should seek guidance from the Director: AMD or the chairperson or vice-chairperson of the relevant committee.

Non-specific interests must be declared prior to appointment to a committee, on an annual basis thereafter or as the need arises and updated prior to each meeting of the committee.

In addition, specific interests must be declared by members and other meeting participants prior to each meeting of a committee in accordance with a time frame determined by the Director: AMD, in consultation with the chairperson or vice-chairperson of a committee.

The importance of declaring interests and the potential consequences of non-disclosure should be discussed in detail with prospective members of a committee prior to appointment or nomination, and with members of a committee on an annual basis. Identification of a conflict of interest will not necessarily prohibit membership or involvement in a committee, but will allow the opportunity to manage conflicts identified appropriately.

Any person requested by a committee to provide information/input that will inform decision-making must declare his/her interests and await a ruling thereon by the relevant assessor of interest before any work is started. This process must be repeated for each request received.

Interests should be declared and documented by all members and other meeting participants by completing a declaration of interest form.

The secretariat of the committee must provide a summary of declaration of interests by members and other meeting participants to the Director: AMD.

7. Assessment of Interests

Assessment of all non-specific declarations of interest must be conducted prior to appointment of members onto a committee and on an annual basis. An assessment of all declarations of interest (specific and non-specific) must be conducted prior to each meeting of a committee. Assessments must be performed in accordance with Appendix 1 to determine if a COI exists and if so, the level of significance. Table 1 provides details of the persons responsible for the assessment of interest of various categories of person.

Table 1: Responsible individuals in assessment of interests

Person declaring interest	**Assessor of Interest**
Prospective member of a committee	Director: AMD or persons responsible for selection or appointment of members of a committee
Member of a committee	Chairperson or vice-chairperson of relevant committee
Meeting participant (who is not a member of the committee)	Chairperson or vice-chairperson of relevant committee
Chairperson	Director: AMD or appointee as specified in the terms of reference of the committee

Person declaring interest	Assessor of Interest
AMD Personnel	Director: AMD
Director of AMD	DDG: NHI

The persons responsible for the assessment of interest may refer a matter related to declaration of interest to the relevant committee for discussion. The interest declared may also be discussed further with the declarer thereof, to obtain more insight or information. Final responsibility for the classification, and management of COIs, rests with the assessor of interest as provided in Table 1. The Director: AMD may consult with the DDG: NHI as needed on interests declared by prospective committee members, committee members or meeting participants.

7.1. Classifying interests

The individual/s responsible for assessment of interest will evaluate the declarations of interest and classify each interest accordingly.

An interest can be classified as 'no conflict'; 'insignificant'; 'potentially significant', or 'clearly significant'. Appendix 1 details the steps to categorise each interest declared, timeframes for declaration, assessment of significance and management according to significance.

The classification will be recorded with a written statement, explaining the reason/s for such classification, and signed by the person/s responsible for the assessment.

8. Management of declared interests

The management of interests includes the recording and monitoring of interests, the actions taken to manage COIs, as well as the management of non-compliance with this policy (See Appendix 1).

Due to the specific duties of the chairpersons of committees, all their interests should be carefully considered and documented before appointment.

8.1. Recording of interests

All declared interests of the chairperson, members and other meeting participants should be collated by the secretariat. Non-specific interests that may be relevant at a specific meeting must be noted in the agenda for discussion at that meeting. Receipt of declarations of interest prior to commencement of a committee meeting should be recorded in the minutes, as well as the actions taken to manage any COIs identified. All new interests and COIs should be added to the record of declared interest at the start of any meeting, and should be included as part of the meeting documentation. Conflicts should be addressed prior to proceeding to other agenda items.

8.2. Monitoring Conflict of Interests

Non-specific and specific interests and classified COIs need to be carefully considered by the assessor/s of interest during the planning of committee activities, as COIs may compromise activity prioritisation of the committee. Before meetings that involve formulation of the committee's project plan, specific interests should be declared and reviewed. In addition, the

record of declared interests should be reviewed for all non-specific and specific interests declared previously. Details regarding who proposed and seconded potential committee activities should be recorded in the minutes.

Once the project plan has been finalised, responsible individuals (Table 1) should assess declared non-specific interests against the project plan, and document any identified COIs that may be relevant to a particular matter.

All interests and COIs relevant to any committee activity must be recorded in the record of declared interests and then reviewed the day before each meeting by the assessors of interest. At the beginning of the meeting, as an agenda item, all newly declared interests and COIs, should be discussed with the committee led by the responsible individual. The agenda should allow for the chairperson, vice-chairperson, AMD personnel or committee members to raise any concerns related to any previously declared interests or COIs.

8.3. Actions for managing Conflicts of Interests

When an interest has been declared and a COI has been identified, the following actions can be carried out by the responsible individual (See Table 1), to manage the COI:

1. **No COI**
   No action required.

2. **Insignificant COI**
   Member or other meeting participant may participate in all applicable facets of meeting provided his/her interests are recorded and he/she provides an undertaking that conflicts or relationships will not bias or influence his/her involvement in committee activities.

3. **Potentially significant COI, but expert insight would benefit decision**
   Member or other meeting participant should have limited involvement or recuse themselves from the particular agenda item, review, appraisal, or decision of committee. The management of potentially significant COI is decided upon by the responsible assessors of interest.

4. **Clearly significant COI**
   Member or other meeting participant should recuse themselves and be excluded from participation in decision making relating to the agenda item in question. The management of clearly significant COI is decided upon by the responsible assessors of interest.

The affected person shall be given the opportunity to clarify his/her position, where after the assessor of interest shall make a decision in the absence of the affected person. Where a clearly significant conflict of interest is likely to recur, despite the mitigating measures applied on previous occasions, the assessor of interest should consider whether it is appropriate for such member to continue to serve on the committee, and make a decision accordingly.

In terms of interests declared by co-opted experts or advisors which are deemed to be significant, the responsible assessor of interest will determine if the work should still be delivered by that individual or whether alternate arrangements should be made.

8.4. Process to manage non-compliance with this policy

Potentially significant and clearly significant COI should be discussed prior to proceeding further with the agenda items of a meeting to determine if a specific member(s) or other meeting participant should be recused from decision-making. This should be managed by the chairperson and documented by the secretariat.

In the event that an individual has failed to declare an interest, a written explanatory statement about the non-disclosure must be provided by the individual and the matter must be investigated by the responsible individual to determine:

- Whether the lack of disclosure was intentional;
- The significance of the undisclosed interest (according to the classification above); and
- If the declared interest directly affected any review, appraisal, recommendation, decision or activity of the committee.

During such an investigation, the member or other meeting participant must recuse him/herself from all committee activities until the investigation is concluded.

On conclusion of the investigation the following actions may be taken in accordance with the terms of reference and in line with applicable legislation.

9. Record and Publication of Declared Interests and Conflicts of Interests

A record of the declared interests and COIs shall be kept at the NDoH including:

- Names of individuals who declared interests on appointment, as the interest first arose or through the annual declaration, and the nature of such interest;
- Names of individuals who have declared interests at meetings - giving dates, names of relevant products and companies, details of the interest declared, whether the member or other meeting participant took part in the proceedings and resulting action that took place regarding management of the COI.

Information disclosed on this form should be included in the minutes of each meeting and may be made available to third parties or disclosed pursuant to a requirement or request by operation of any applicable law, regulation or court order.

Summarised annual declarations of interest should be published on the NDoH website. A rolling form of specific COIs declared at each meeting, as well as changes to non-specific COIs, should also be maintained by the Committee Secretariat and published on the NDoH website.

Where a technical document is developed for the committee and published, such as a medicine review, the individual/s responsible for the document should have relevant summarised declarations of interest included as part of the document.

10. Roles and Responsibilities

Individual	Roles and Responsibilities
Assessor/s of Interest	• Ensure that the declarations of interest of members and other meeting participants have been received upon appointment, annually and at each committee meeting; and • Assess the potential COI declared by an individual in line with this policy.
Committee Secretariat	• Administer declaration of interest forms and ensure that the declarations of interest of members and other meeting participants have been received upon appointment, annually and at each committee meeting, as applicable; • Record, store and publish declarations of interest in line with this policy; • Declare their own actual and potential COIs; and • Ensure recusal of committee members and meeting participants occurs (as appropriate) during decision-making and adequate documentation of such action.
Committee members and other meeting participants	• Declare all potential interests in line with this policy before appointment to a committee, annually and at every committee meeting, as applicable.
Senior Management of AMD	• Assess and manage potential interests of members prior to joining a committee, as well as declaring their own actual and potential COIs, as outlined in section 7.

11. Related Documents

- Terms of reference of committees operating under the auspices of AMD
- National Essential Medicines List Committee Declaration of Interests Guidance Document (also applicable to Expert Review Committees)
- Confidentiality Guideline for committees operating under the auspices of AMD

12. Sources

1. National Department of Health. Declaration of Interests Guidance Document: A code of practice for the National Essential Medicines List Committee, members of technical expert review committees [Internet].
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6. National Institute for Health and Care Excellence (NICE). Policy on Conflicts of Interest [Internet]. 2014 [cited 2017 Sep 21]. Available from: https://www.nice.org.uk/media/default/about/who-we-are/policies-and-procedures/code-of-practice-for-declaring-and-managing-conflicts-of-interest.pdf.
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10. Australian Government Department of Health Therapeutic Goods Administration, Conflicts of interest and confidentiality obligations "Guidance for TGA advisory committee members". Version 2.0, May 2018

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

- *Review question we addressed (PIC elements)*
- *We searched on X date and where*
- *We found X reviews and Y trials – short description*
- *Key outcomes summary – particularly outcomes driving the decision*
- *Additional factors: costs, feasibility, access – if these are important to decision*
- *Implication for practices*

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)

PROSPERO registration: CRD42021286710

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

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