METHODS GUIDE FOR RAPID REVIEWS FOR COVID-19 MEDICINE REVIEWS

Rationale for rapid reviews

In the context of the COVID-19 National Disaster declared in South Africa, there is urgency to ensure that clinical guidance for all sectors of the country is based on the best available research evidence.

Systematic reviews underpin policy and practice decisions, but in the current times, we must ensure responsive, time-sensitive reviews that inform health decision makers as fast as possible, while ensuring that the scientific imperative of methodological rigor is satisfied. Increasingly rapid reviews are conducted when there is urgency to respond and make decisions where evidence is uncertain. Where systematic reviews have planned questions and methods and recognised steps to minimize bias in their reporting, rapid reviews may omit key steps that may introduce bias. The below methods guide aims to standardize rapid reviews and ensure a rigorous product is used to inform healthcare decisions in the best interests of people in South Africa.

Rapid reviews overseen by the NELMC on COVID-19 Therapeutics are specifically to inform the national COVID-19 clinical guidelines, government, clinicians and patients. The reviews aim to be completed within 7-10 days from agreement on the question.

METHODS GUIDE
1. Clarify scope and question
Guideline questions can be formulated with this format: *SHOULD "X" USED COMPARED TO "Y" BE USED FOR PREVENTION/ MANAGEMENT OF COVID-19?* - <u>POPULATION</u> Population considered according to **ambulatory; hospitalised; and subsets of hospitalised patients requiring either oxygen or ventilatory support ; prophylaxis** Where appropriate, the review may include patients with other forms of respiratory illness, e.g. MERS, SARS-COV - <u>INTERVENTION</u>: <u>MEDICINE AND FORMULATION</u> (dose/frequency, mode of delivery, and any co-treatments) Intervention of interest either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease. - Any comparator, active or placebo - <u>OUTCOMES</u> *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/ pre-hospital** Ambulant patients with confirmed COVID-19, no restriction to age but disease sufficiently mild that management outside hospital is feasible. **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.

Population 2 – hospitalised
Patients with confirmed COVID-19, no restriction to age but disease severity such that hospitalisation required.
Outcomes
Mortality; duration of 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; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay; duration of mechanical ventilation; adverse reactions.

Population 3 – i)requiring oxygen or ii)ventilatory support
Patients with confirmed COVID-19, no restriction to age but severe disease requiring i)oxygen or ii)ventilatory assistance.
Outcomes
Mortality; duration of ventilatory support; progression to mechanical ventilation; duration of ICU stay; duration of mechanical ventilation; adverse reactions.

Population 4 – prophylaxis
Patients at risk of COVID-19 but currently asymptomatic, no restriction to age or comorbidities
Outcomes
Development of COVID-19 with positive SARS-CoV-2 PCR; duration of symptoms; proportion requiring hospitalisation; adverse reactions.

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

2. Study designs to identify

- Systematic reviews of trials
- Where not available, seek controlled clinical trials in patients
- Where no controlled clinical trials available, seek non-randomised controlled studies and where none of the above are available, single arm cohorts, case series may be reported
- Where helpful, extract information from relevant guidelines
- If WHO has issued guidance – check for evidence reviews underpinning their decision

Ongoing trials list from Cochranes COVID-19 Register of studies (https://covid-19.cochrane.org/ - this lists planned and ongoing studies from WHO's International Clinicals Trials Registry Platform ICTRP.

3. Search approach

Systematic search of at least two databases for studies or planned trials.

- Search for systematic reviews: 1) Epistemonikos (https://www.epistemonikos.org/en/), 2) Cochrane library; 3) Network Meta-analysis website (www.covid-nma.com) – the latter site now includes living reviews of pharmacological agents including trial appraisal and meta-analysis that can be used.
- Search for other studies:1) PubMed; 2) Cochrane COVID-19 register (https://covid-19.cochrane.org/)
- Search for planned and ongoing studies: Cochrane COVID-19 register (https://covid-19.cochrane.org/)

4. Selecting studies for inclusion

- Screening of title and abstract from search output done in duplicate
- Full-text screening in duplicate

Where very rapid turnaround, this may only have a single reviewer.

5. Data extraction

This may be done by one reviewer, checked by a second reviewer

- Study design [including methods, location, sites, groups]
- Setting
- Participant characteristics [specify, with a focus on effect modifiers and prognostic factors] any disease severity and age, co-morbidity especially cardiovascular, HIV, TB, respiratory
- Intervention characteristics [specify details]
- Comparator characteristics
- Outcomes assessed
- Numerical data for outcomes of interest

Relevant records will be extracted by a single reviewer and checked by a second reviewer and reported in a table of included studies with all key characteristics.

6. Appraisal of study quality

Systematic review:
- Where systematic review/s found, appraise the quality using AMSTAR2 (Shea 2017). Online checklist found here: https://amstar.ca/Amstar-2.php (Appendix 1)

Primary studies:
- For randomised controlled trials assess risk of bias using the standard Cochrane risk of bias assessment tool 2.0 which considers: random sequence generation, allocation concealment, blinding of participants, personnel and outcomes, incomplete outcome data, selective outcome reporting and other sources of bias (https://training.cochrane.org/handbook/current/chapter-08) or another standard tool. Where possible, develop graphic representations of potential bias within and across studies using RevMan 5.3.5 (Review Manager) or other software.

- Appraisal of non-randomised studies may use relevant tools, e.g. CEBM Oxford appraisal tools or be reported narratively.

Colleagues from Cochrane France, Ireland and Germany and other collaborators are conducting living systematic reviews of interventions including appraisals and forest plots that may be included rather than developed de novo. These are found here: www.covid-nma.com

7. Data synthesis

i) We will appraise and summarise results of a systematic review, where available.
ii) We will appraise and summarise controlled clinical trials narratively, unless there is capacity to conduct synthesis within the one week time frame.
- We will only conduct a meta-analysis if the included studies are sufficiently homogeneous in terms of design, population, interventions and comparators reporting the same outcome measures. The results for clinically homogeneous studies will be meta-analysed using RevMan (Review Manager).
- Meta-analyses will be conducted using the inverse variance method. A random effect model will be used. Separate meta-analyses will be presented for specific populations or interventions if statistically significant heterogeneity is explained by some of these, or if a convincing subgroup effect is found.
- For any outcomes where insufficient data are found for a meta-analysis, a narrative synthesis will be presented.
iii) We will summarise observational studies and case series in a table format

iv)   Grading the quality (or certainty) of the evidence

- Where possible, and we find systematic reviews that include reporting using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, we will present those findings. GRADE aims to provide a sensible and transparent approach to grading quality (or certainty) of evidence and the strength of recommendations.
- GRADE considers not only the risk of bias (appraisal of internal validity), but also whether the evidence is consistent across studies, directly applicable to the PICO, precise with adequate events and sample size and whether publication bias is possible.

8. Draft and finalise report with key findings and recommendations

Reports should be completed in the rapid review template (Appendix 3).

- Lead reviewer and the review team may draft the key findings and recommendations
- Peer review of the review by the Committee
- Final review disseminated to NDoH Executive Management, the COVID-19 Clinical Guideline Committee, MAC on OCVID-19, Vaccine MAC and other interested stakeholders and posted on the open access website: http://www.health.gov.za/covid-19-rapid-reviews/

Rationale for adolopment of other clinical guidelines

In order to minimise duplication of efforts, where up-to-date clinical practice guidelines have already been developed to answer specific prioritized research questions, the NEMLC on COVID-19 Therapeutics may opt to adapt the guidelines for local use.

The guidelines should be assessed to be of sufficient quality, using the AGREE 2 tool (Bouwer 2010).

The methodology is based on the GRADE-ADOLOPMENT approach proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (Schünemann 2017).

The populated GRADE Evidence To Decision table for the specific clinical guideline is reviewed on the GRADEPro website (https://gradepro.org), and the categories are contextualized for South Africa.

These categories are:
- Is there a problem priority?
- What is the overall certainty of this evidence?
- Is there important uncertainty about how much people value the main outcomes?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?
- Are the resources required small?
- Is the incremental cost small relative to the net benefits?
- What would be the impact on health inequities?
- Is the option acceptable to key stakeholders?
- Is the option feasible to implement?

Judgements for each category are agreed upon through consensus decision-making by the NEMLC on COVID-19 Therapeutics, and a recommendation is made.

Appendix 1: Evaluating the methodological quality of systematic reviews – AMSTAR 2 tool (Shea 2017)

No.	Criteria	Yes/ Partial Yes/ No
1	Research questions and inclusion criteria for the review included the components of PICO	
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	
3	Review authors explained selection of the study designs for inclusion in the review	
4*	Review authors used a comprehensive literature search strategy	
5	Review authors perform study selection and data extraction in duplicate	
6	Review authors provided a list of excluded studies and justify the exclusions	
7*	Review authors described the included studies in adequate detail	
8	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	
9*	Review authors reported on the sources of funding for the studies included in the review?	
10	For meta-analyses, review authors used appropriate methods for statistical combination of results	
11*	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	
12	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	
13*	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	
14	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	
15*	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	

Critical domains:
2: Protocol registered before commencement of the review
4: Adequacy of the literature search
7: Justification for excluding individual studies
9: Risk of bias from individual studies being included in the review
11: Appropriateness of meta-analytical methods
13: Consideration of risk of bias when interpreting the results of the review
15: Assessment of presence and likely impact of publication bias

Rating overall confidence in the results of the review
• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies
(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

Appendix 2: Template for rapid review report – refer to the Terms of Reference

PROSPERO registration: CRD42021286710

Version	Date	Revisions
1.0	31 May 2020	N/A; Initial version
2.0	9 March 2021	AMSTAR checklist updated to version 2 (Shea 2017)
3.0	15 September 2021	NEMLC Therapeutic Guidelines Subcommittee on COVID-19 reconstituted to ministerial appointed NEMLC on COVID-19 Therapeutics Adolopment process included
4.0	12 March 2022	PROSPERO registration number added