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 decisionmakers 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 Sub-committee for the COVID-19 Clinical Guidelines Committee 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?* - POPULATION 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 - INTERVENTION: MEDICINE AND FORMULATION (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 - OUTCOMES *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 – 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 – requiring oxygen or ventilatory support
Patients with confirmed COVID-19, no restriction to age but severe disease requiring oxygen or 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 AMSTAR. Online checklist found here: https://amstar.ca/Amstar_Checklist.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 Subcommmittee
- Final review disseminated to the COVID-19 Clinical Guideline Committee, MAC and other interested stakeholders and posted on the open access website: http://www.health.gov.za/index.php/national-essential-medicine-list-committee-nemlc/category/633-covid-19-rapid-reviews

Appendix 1: Evaluating the methodological quality of systematic reviews - AMSTAR tool (Shea 2009)

No.	Criteria	Yes/ No/ Unclear/ not applicable
1	Was an ‘‘a priori’’ design provided? The research question and inclusion criteria should be established before the conduct of the review.	
2	Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	
3	Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated, and where feasible, the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	
4	Was the status of publication (i.e., grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	
5	Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	
6	Were the characteristics of the included studies provided? In an aggregated form, such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The ranges of characteristics in all the studies analysed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	
7	Was the scientific quality of the included studies assessed and documented? ‘‘A priori’’ methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant.	
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	
9	Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).	
10	Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	
11	Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	

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