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

TITLE: Should baricitinib be used to treat COVID-19?

Date: 19 November 2021 (update of original 15 October 2021 rapid review report)

Key findings

- This rapid review reports the available evidence about the benefits and harms of baricitinib for treating patients aged 18 years and older hospitalised with COVID-19.
- We searched relevant medical literature up to 17 September 2021.
- We identified one eligible study: a randomised placebo-controlled trial conducted in 12 countries globally (Marconi et al.), which enrolled 1525 hospitalised COVID-19 participants, 1232 of whom required supplemental oxygen.
- There was no significant difference in the primary outcome, a composite of progression to high-flow oxygen, non-invasive ventilation, invasive ventilation (including ECMO), or death, by Day 28: odds ratio: 0.85, 95% CI 0.67 to 1.08). Baricitinib reduced all-cause mortality at Day 28 (hazard ratio (HR) 0.57; 95% confidence interval (CI) 0.41 to 0.78) (moderate certainty evidence). The number needed to treat to prevent 1 death was thus 20 (95% CI 13 to 37).
- There were no significant differences in progression to requiring oxygen or ventilation (HR 0.89; 95% CI 0.74 to 1.06, moderate certainty evidence) or duration of ICU stay (mean difference 0.02 days; 95% CI -0.62 to 0.65, high certainty evidence).
- There were no differences in adverse events (relative risk (RR) 1.00; 95% CI 0.89 to 1.12, high certainty evidence) or serious adverse events (RR 0.81; 95% CI 0.64 to 1.02, moderate certainty evidence).
- Overall the trial was assessed as high quality and the benefits of baricitinib outweighed the risks.

NEML MAC 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	

Recommendation: The Committee suggests baricitinib for use in hospitalised patients with confirmed COVID-19 who require oxygen and have at least one raised inflammatory marker. This recommendation is conditional on baricitinib being accessible to all eligible public sector patients in South Africa.
Rationale: Baricitinib reduced mortality in a single study, and was not associated with an increased risk of adverse events. It is cheaper than tocilizumab, and may be administered orally (or via nasogastric tube). However, the committee is concerned that cost may result in inequitable access, and there is uncertainty regarding supply.
Level of Evidence: Moderate certainty evidence
Review indicator: Equitable funding; results of further RCTs; confirmation of adequate supply

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

NEML MAC on COVID-19 Therapeutics: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen, Andy Gray, Tamara Kredo, Renee De Waal, Jeremy Nel, Helen Rees.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

BACKGROUND

In patients infected with SARS-CoV-2, disease severity and outcomes are related to the characteristics of the immune response. [1-6] The median time from onset of symptoms of COVID-19 to the development of acute respiratory distress syndrome (ARDS) is as short as 8 days. [7] Interleukin (IL)-6 and other components of the inflammatory cascade play an important role in the inflammatory reaction and immune response. [8] However, excessive cytokine production ('cytokine storm') as part of a hyperinflammatory response has been suggested as a cause of severe COVID-19. [1-3]

Baricitinib is a Janus kinase inhibitor that has anti-inflammatory properties. [8] Baricitinib is registered for the treatment of several dermatological conditions and rheumatoid arthritis [9-10]. Several observational studies of hospitalised patients with COVID-19 showed evidence of clinical improvement with baricitinib. [11-13] It reduces levels of multiple cytokines associated with the pathophysiology of COVID-19 disease, as well as having anti-viral activity. [14] In a phase 3 double-blind, randomised controlled trial in hospitalised COVID-19 patients, treatment with baricitinib plus remdesivir was found to reduce time to recovery (rate ratio 1·16 [95% CI 1·01–1·32]) and was associated with fewer adverse events compared to treatment with remdesivir alone, although there was no significant difference in mortality at 28 days between the two groups (5·1% with baricitinib and remdesivir vs 7·8% with remdesivir); [HR] 0.65 (95% CI 0.39 to 1.09).[15]

Current only a few guidelines include recommendations regarding baricitinib use; the WHO has not issued guidance yet. The Federal Drug Authority (FDA) in the USA recently issued 'emergency use authorization' for baricitinib (https://www.fda.gov/media/143823/download), which states: '*to permit the emergency use of baricitinib for treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).*' However, baricitinib is not yet approved by the FDA through its traditional mechanisms. The Australian National COVID-19 Clinical Evidence Taskforce (https://covid19evidence.net.au/) have issued a conditional recommendation for the use of baricitinib as follows: '*Consider using baricitinib for adults hospitalised with COVID-19 who require supplemental oxygen, high-flow oxygen and/or non-invasive ventilation*.' They suggest that baricitinib be used only in the context of research when given to pregnant woman and children. Guidelines in India (https://indiacovidguidelines.org/baricitinib/) have the following recommendation: *'Baricitinib is not recommended in patients that do not have hypoxia (strong recommendation). In patients with hypoxia who have moderate, severe or critical illness, clinicians may wish to consider adding baricitinib to steroids, if not on tocilizumab (conditional recommendation). Tocilizumab and baricitinib should not be given together.'*

RESEARCH QUESTION: What is the efficacy and safety of baricitinib for the treatment of hospitalised patients with confirmed COVID-19 regardless of their oxygen requirements?

METHODS

We searched four electronic databases: Cochrane Library COVID-19 study register, PubMed, and the Epistemonikos LOVE platform on 7 September 2021; and the COVID-NMA Living review database on 7 September 2021. Cochrane, Epistemonikos and COVID-NMA systematically search PubMed, Embase, MedRxiv, WHO's ICTRP, and clinicaltrials.gov. The full search strategy can be found in Appendix 1.

The retrieved records were imported into the Covidence software for title and abstract, and full text, screening. Screening of records, selection of articles and data extraction was done independently and in duplicate by two reviewers (VN and NB) with conflict resolution by a third reviewer (TK). The main characteristics of the included study and study outcomes are shown in Table 1. Two reviewers used the Cochrane ROB 2.0 tool to appraise the risk of bias in the included trial. For dichotomous outcomes, results were presented as results from the trial report (e.g., hazard ratios. HR) where available or from the Living Systematic Review on the www.covid-nma.com website. We reported risk ratios (RR) for dichotomous data and mean differences for continuous outcomes with 95% confidence intervals (CI). GRADE was used to assess the overall confidence of the evidence considering various factors that may decrease

our confidence in the trial finding including risk of bias, inconsistency, imprecision, publication bias and indirectness. [16] Table 2 summarises the evidence profiles, and Table 3 reports the quality appraisal of the included trial.

Eligibility criteria for review

Population: Hospitalised patients with COVID-19 (whether requiring oxygen therapy or not); no restriction to age or co-morbidity.

Intervention: Baricitinib, alone or in combination with any other agent; no restriction on dose, frequency, or timing with respect to onset of symptoms.

Comparators: Standard of care +/- placebo.

Outcomes: Mortality; duration of ventilatory support including mechanical ventilation; duration of ICU stay; progression to ICU admission, progression to mechanical ventilation or requiring oxygen, clinical outcome on an ordinal scale, adverse events, adverse reactions.

Study designs: Randomised controlled trials and systematic reviews of randomised controlled trials.

RESULTS

Results of the search

The database search identified 127 records. Following the removal of duplicates, 107 titles and abstracts and then 43 potentially eligible full-text records were screened against the PICO. Of the 43 full-text records, 42 were excluded. One RCT was eligible for inclusion in the review. Study selection is shown in the Prisma flow graphic as Figure 1.

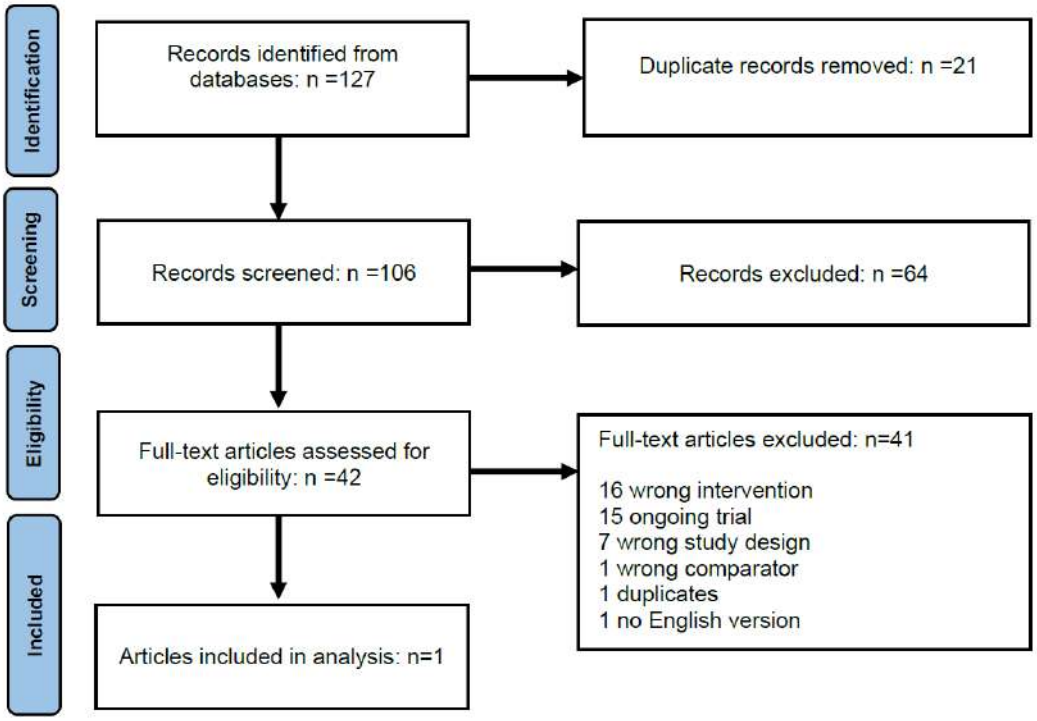


Figure 1: PRISMA flow diagram for the review

Excluded studies

We excluded 41 studies, mostly because they didn't evaluate baricitinib, they were ongoing studies, or they were the wrong study design. One notable exclusion was the ACTT-2 trial, which evaluated baricitinib plus remdesivir compared with remdesivir. Steroid use was allowed only if part of a written treatment policy at the hospital, or for indications other than COVID-19. Steroids were used by 56/515 (11%) patients in the baricitinib plus remdesivir arm and 67/518

(13%) patients in the remdesivir arm. The study was excluded as it involved an active comparator that is not the standard of care in South Africa, and the majority of the patients did not receive current standard of care (corticosteroids for those who require oxygen).

Description of the included study

Marconi et al., 2021, enrolled 1525 participants from 12 countries in Asia, Europe, North America, and South America in a randomised controlled trial. Participants were eligible if they were aged at least 18 years at enrollment; were hospitalised with COVID-19 infection confirmed by polymerase chain reaction (PCR) test; and had at least one elevated inflammatory marker[17]. In October 2020 the inclusion criteria were changed to include only participants requiring oxygen. Potential participants who were pregnant or intended to become pregnant or were breastfeeding were excluded. 1232 patients required oxygen at baseline. Participants were randomised to receive 4 mg/day of baricitinib or placebo, administered orally or via nasogastric tube for 14 days, combined with standard of care. Standard of care included systemic corticosteroids in 1204 participants (79%) and remdesivir in 287 (19%). The intention-to-treat analysis was conducted in two populations: population 1 (comprising all randomised participants) and population 2 (participants who required oxygen supplementation at baseline and were not receiving systemic corticosteroids for COVID-19).

Table 1 summarises the characteristics and results of the included trial.

The primary outcome of the study was a composite of progression to high-flow oxygen, non-invasive ventilation, invasive ventilation (including ECMO), or death, by day 28. There was no significant difference in the primary outcome, which occurred in 27.8% of patients in the baricitinib arm, and 30.5% in the placebo arm (odds ratio: 0.85, 95% CI 0.67 to 1.08). The study reports 17 secondary outcomes altogether and did not adjust these analyses for multiplicity.

The included trial refers to the following ordinal scale for assessing COVID-19 severity:

The National Institute of Allergy and Infectious Disease Ordinal Scale (NIAID-OS)[6] classifies COVID-19 patients into the following categories: OS 1 Not hospitalized, no limitations on activities, OS 2 Not hospitalized, limitation on activities and/or requiring home oxygen, OS 3 Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care, OS 4 Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care, OS 5 Hospitalized, requiring supplemental oxygen, OS 6 Hospitalized, on non-invasive ventilation or high-flow oxygen devices, OS 7 Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) and OS 8 Death.

Appraisal of the trial

Overall, the trial was judged to be of high quality. A computer-generated random sequence was used to randomise participants; and the intervention was placebo controlled. There was a low risk of deviations from the intervention, as outcome assessors, participants and personnel were blinded to the allocation. The analysis followed intention-to-treat principles. There was substantial missing outcome data, which is clearly outlined in the trial Prisma flow diagram. Fourteen and 9 participants were lost before receiving a dose of medicine in the baricitinib and placebo groups, respectively, and a further 106 and 148 in the baricitinib and placebo arm, respectively, discontinued treatment early because of death, adverse events, loss to follow up, or withdrawal. After receiving at least one dose of study treatment, loss to follow up occurred in 20 and 22 participants, and withdrawal occurred in 12 and 7 participants, in the baricitinib and placebo arm, respectively. Overall, differences were balanced between the trial arms. The risk of selective reporting was low given that the protocol, statistical analysis, and registries were available for review, although there were changes in the outcomes chosen between the initial protocol and final version. All domains were judged to have low risk of bias warranting an overall assessment of low risk of bias (Table 3).

Effects of intervention(s)

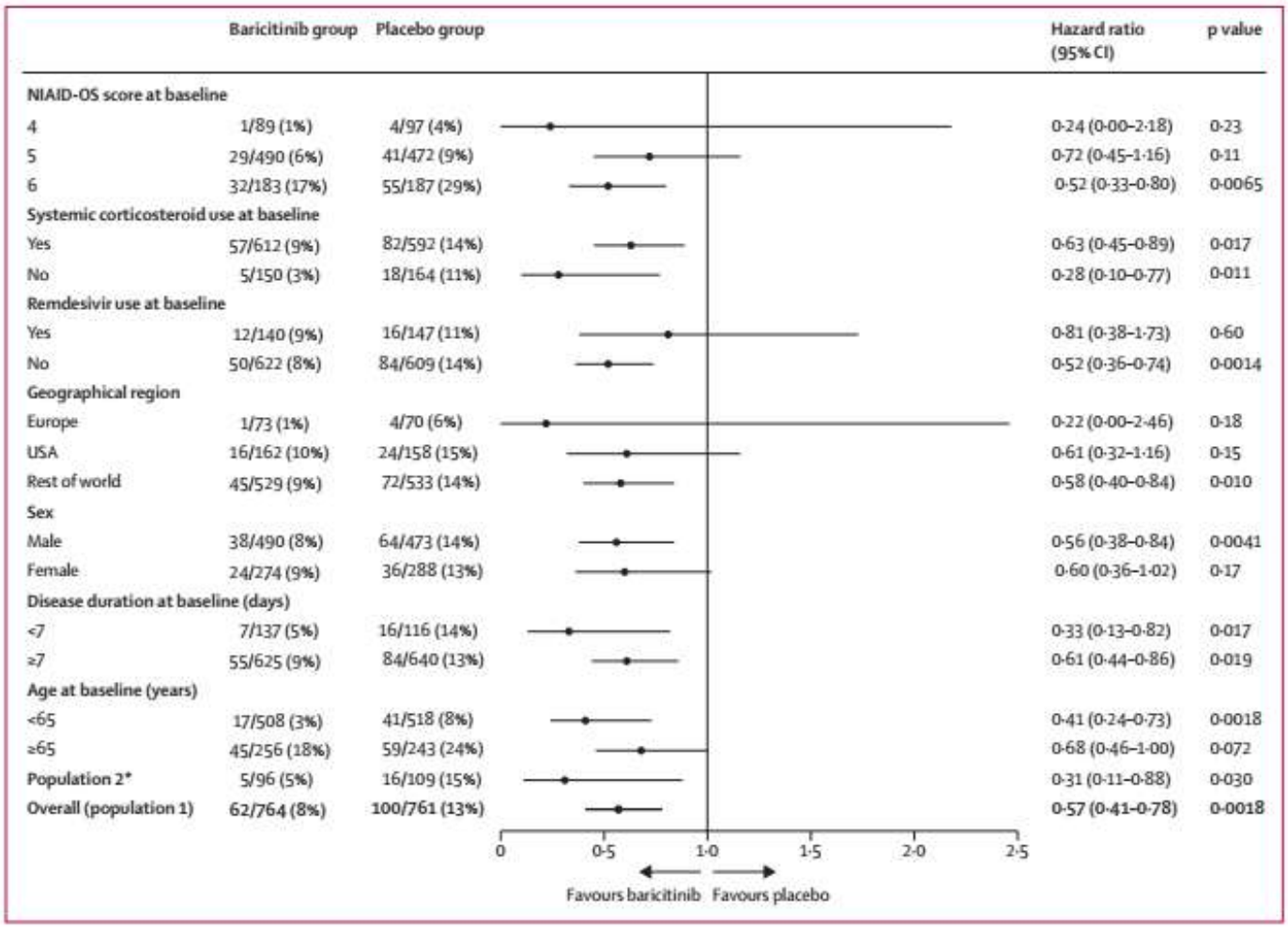
Table 2 summarises the results and Table 3 outlines the quality appraisal of the included trial.

1. Mortality

The risk of 28-day all-cause mortality was reduced with baricitinib by 43% (HR 0·57; 95% confidence interval (CI) 0·41–0·78], equivalent to 54 fewer deaths per 1000 (95% CI from 27 fewer to75 fewer). One additional death was thus prevented per 20 participants treated with baricitinib. This evidence was considered to be of moderate certainty.

There was a 38% reduction in 60-day all-cause mortality with the use of baricitinib (HR 0·62; 95% CI 0·47–0·83), with an absolute risk difference of –4·9 percentage points.

Figure 2 shows the 28-day all-cause mortality by sub-group. Baricitinib reduced mortality by 48% (HR 0.52; 95 CI 0·33–0·80) for those requiring supplemental oxygen on non-invasive ventilation or high-flow oxygen devices. Baricitinib reduced mortality regardless of systemic corticosteroid use, age, or duration of illness.



Footnote: HRs and 95% CIs were calculated with a Cox proportional hazards model. The treatment effect was adjusted by all baseline randomisation factors, except when redundant (e.g., for age group [<65 or ≥65 years] in the age subgroup analyses). HR=hazard ratio. NIAID-OS=National Institute of Allergy and Infectious Disease Ordinal Scale. *Participants who, at baseline, required oxygen supplementation and were not receiving dexamethasone or other systemic corticosteroids for the primary study condition [17]

Figure 2: Forest plot of Day 28 all-cause mortality by subgroup

2. **Progression to mechanical ventilation or requiring oxygen (**one category increase on NIAID-OS)

   The study reported this outcome as a one category increase on the NIAID ordinal scale. There was a trend for baricitinib to reduce the risk of progression to high flow oxygen, non-invasive ventilation, invasive mechanical ventilation by day 28 in those who receive baricitinib 229/764 (30.0%) compared to placebo 253/761 (33.2%) (HR 0·89; 95% CI 0.74–1.06) (moderate certainty evidence). That is equivalent to 30 fewer people with clinical deterioration per 1000 who receive baricitinib (from 74 fewer to 16 more).

3. **Duration of ventilatory support**

   The study reported days of supplemental oxygen use. There was no difference in the duration of oxygen use among those who received baricitinib (4.37 days; SD 0.22) compared to those receiving placebo (4.6 days; SD 0.22). The

mean difference was 0.23 days (95% CI 0.68 0.21). This was assessed as high certainty evidence.

4. **Duration of ICU stay**
   There was no difference in the duration of stay in ICU among those receiving baricitinib (3.19 days; SD 0.32) compared to the placebo group (3.17 days; SD 0.31). The mean difference was 0.02 days (95% CI -0.62 to 0.65). This was assessed as high certainty evidence.

5. **Progression to ICU admission**
   The trial did not report on this outcome.

6. **Clinical outcome on ordinal scale (follow-up: 28 days)**
   The study reported this outcome as an improvement of ≥2 points on the NIAID ordinal scale. There was no difference between clinical improvement by 28 days with baricitinib (593/764; 77.6%) compared to placebo (592/761; 77.8%; RR 1.00; 95% CI 0.95-1.05). This was assessed to be high certainty evidence.

7. **Adverse events**
   There was no difference in the number of adverse events between the baricitinib group (334/764; 43.7%) compared to placebo (334/761; 43.9%; RR 1.00; 95% CI 0.89 to 1.12). This was assessed to be high certainty evidence.

8. **Serious adverse events (SAEs)**
   There was a trend to fewer SAEs in the baricitinib arm (110/764; 14.4%) compared to the standard of care arm (135/761; 17.7%; RR 0.81; 95% CI 0.64 to 1.02). This was assessed as moderate certainty evidence. There were probably 34 fewer SAEs per 1000 people treated with baricitinib (ranging from 64 fewer to 4 more per 1000).

9. **Adverse reactions**
   The trial did not report on this outcome.

CONCLUSION

One randomised controlled study of baricitinib in hospitalised patients, most of whom required oxygen, demonstrated that the risk of 28-day all-cause mortality was reduced with baricitinib by 43% (HR 0·57; 95% CI 0·41–0·78], equivalent to 54 fewer deaths per 1000 (95% CI from 27 fewer to 75 fewer). Baricitinib reduced mortality regardless of systemic corticosteroid use, age, or duration of illness. There was no impact on duration of requirement for ventilatory support or time in ICU. Adverse events and serious adverse events were not increased in participants on baricitinib.

Reviewers: Marc Blockman, Renee de Waal, Ntombifuthi Blose, Veranyuy D Ngah, Tamara Kredo.

Declaration of interests: MB (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town). and RdW (Centre for Infectious Disease Epidemiology and Research, University of Cape Town) have no interests to declare in respect of baricitinib. TK (Cochrane South Africa, South African Medical Research Council (SAMRC); Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostats, Department of Global Health, Faculty of Medicine and health Sciences, Stellenbosch University; TK is co-director of the South African GRADE Network and TK, NB and VDN are partly supported by the Research, Evidence and Development Initiative (READ-It) project and the Collaboration for Evidence Based Health Care and Public Health in Africa COVID-19 project funding (CEBHA+). READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies.)

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Table 1. Characteristics of included trials

Citation	Study design	Population (n)	Treatment and comparison	Main findings	Risk of Bias
Marconi V, et., al Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial, The Lancet Respiratory Medicine, 2021, ISSN 2213-2600, https://doi.org/10.1016/S2213-2600(21)00331-3.	Randomised (1:1) double-blinded, placebo-controlled, parallel-group, phase 3 trial Date: June 11, 2020, to Jan 15, 2021 Setting: Multicenter Follow up: 14 days	Asia, Europe, North America, and South America. Population 1: All randomly allocated participants Population 2: Subpopulation on oxygen and not receiving steroids at baseline N=1525 [Baricitinib group (n=764), placebo group (n=761)] Mean (sd) age: 57.6 (14.1) Baricitinib 57.8 (14.3); Placebo 57.5 (13.8) <65 years: 508/764 (66%) in baricitinib and 518/761 (68%) placebo ≥65 years: 256/764 (34%) in baricitinib and 243/761 (32%) placebo Sex: Overall-: 963 (63.1%) were male. baricitinib (males: 490/764 (64%) females: 274/764 (36%); placebo (males: 473/761 (62%) females: 288/761 (38%)	Intervention: Baricitinib at 4 mg/day; however, 2 mg/day to patients with baseline eGFR of 30 to less than 60 mL/min/1·73 m² + SOC (corticosteroids, antivirals, prophylaxis for venous thromboembolic events) Delivery: oral or crushed for nasogastric tube Comparison: Placebo + SOC	28-day all-cause mortality: Population 1: 8% (n=62) for baricitinib and 13% (n=100) for placebo (hazard ratio [HR] 0·57 [95% CI 0·41–0·78]; nominal p=0·0018), a 43% relative reduction in mortality; one additional death was prevented per 20 baricitinib-treated participants. Population 2: 28-day all-cause mortality was 5% (five of 96 participants) in the baricitinib group and 15% (16 of 109) in the placebo group, equating to a 69% relative reduction (HR 0·31 [95% CI 0·11–0·88], nominal p=0·030 60-day all-cause mortality: was 10% (n=79) for baricitinib and 15% (n=116) for placebo (HR 0·62 [95% CI 0·47–0·83]; p=0·0050) Serious adverse events: (110 [15%] of 750 in the baricitinib group vs 135 [18%] of 752 in the placebo group), serious infections (64 [9%] vs 74 [10%]), and venous thromboembolic events (20 [3%] vs 19 [3%]) were similar between the two groups. Progression to high-flow oxygen &Non-invasive ventilation & mechanical ventilation (MV) or extracorporeal membrane oxygenation (ECMO): "the proportion of patients who progressed to high-flow oxygen, non-invasive ventilation, invasive	Some concerns: For the selection of the reported results - "The prospective registry was available. The protocol and statistical analysis plan is available from the investigators upon request. Mortality measured on day 28 was pre-specified. Results were not selected from multiple outcome measurements or analyses of the data. Outcome analyzed as pre-specified. Risk assessed to be low for the outcome: Mortality (D28). Clinical improvement, time to death, and adverse events were not pre-specified. No information on whether the result was selected from multiple outcome measurements or analyses of the data. Trial probably not analyzed as pre-specified. Risk assessed to be some concerns for the outcomes: Time to death. Clinical improvement (D28). Time to clinical improvement. Adverse

Citation	Study design	Population (n)	Treatment and comparison	Main findings	Risk of Bias
				mechanical ventilation, or death by day 28 (the composite primary endpoint) was 27·8% in the baricitinib group and 30·5% in the placebo group (odds ratio [OR] 0·85 [95% CI 0·67–1·08], p=0·18" - all randomly allocated participants	events. Serious adverse events." [18]

Table 2: Summary of findings

Question: Baricitinib compared to standard care for COVID-19

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	baricitinib	SOC	Relative (95% CI)	Absolute (95% CI)	
Mortality (follow-up: 28 days)											
1	randomised trials	not serious	not serious	not serious	serious[a]	none	62/764 (8.1%)	100/761 (13.1%)	**HR 0.57** (0.41 to 0.78)	**54 fewer per 1,000** (from 75 fewer to 27 fewer)	⊕⊕⊕◯ Moderate
Clinical deterioration - one category increase on NIAID-OS [surrogate for progression to mechanical ventilation or requiring oxygen]											
1	randomised trials	not serious	not serious	not serious	serious [b]	none	229/764 (30.0%)	253/761 (33.2%)	**HR 0.89** (0.74 to 1.06)	**30 fewer per 1,000** (from 74 fewer to 16 more)	⊕⊕⊕◯ Moderate
Days of supplemental oxygen use [surrogate for duration of ventilatory support]											
1	randomised trials	not serious	not serious	not serious	not serious	none	764	761	-	Mean **0.23 Days** (0.68 lower to 0.21 higher)	⊕⊕⊕⊕ High
Duration of ICU stay											
1	randomised trials	not serious	not serious	not serious	not serious	none	764	761	-	Mean **0.02 Days more** (0.62 lower to 0.65 higher)	⊕⊕⊕⊕ High
Clinical improvement >2 points on NIAID-OS scale [surrogate for clinical outcome on ordinal scale] (follow-up: 28 days)											
1	randomised trials	not serious	not serious	not serious	not serious	none	593/764 (77.6%)	592/761 (77.8%)	**RR 1.00** (0.95 to 1.05)	**0 fewer per 1,000** (from 39 fewer to 39 more)	⊕⊕⊕⊕ High
1	randomised trials	not serious	not serious	not serious	not serious	none	334/764 (43.7%)	334/761 (43.9%)	**RR 1.00** (0.89 to 1.12)	**0 fewer per 1,000** (from 48 fewer to 53 more)	⊕⊕⊕⊕ High
Serious adverse events											
1	randomised trials	not serious	not serious	not serious	serious [b]	none	110/764 (14.4%)	135/761 (17.7%)	**RR 0.81** (0.64 to 1.02)	**34 fewer per 1,000** (from 64 fewer to 4 more)	⊕⊕⊕◯ Moderate
Progression to ICU admission - not reported											
Adverse effects - not reported											

CI: confidence interval; **HR:** hazard Ratio; **RR:** risk ratio

Explanations

a. We downgraded by one level for serious imprecision. We calculated calculated the optimal information size for this outcome to check whether it was adequately powered, we found that 1584 patients are required to have a 90% chance of detecting, as significant at the 5% level, a decrease in the primary outcome measure from 13.1% in the control group to 8.1% in the experimental group. The available sample size was 764 in Baricitinib and 761 in the control groups (n = 1525). It is worth noting that there was substantial, but similar loss to follow up in the groups, 20 and 22 in the baricitinib and control respectively.

b. Downgraded by one level for serious imprecision - confidence interval spans appreciable benefit and the null.

Table 3. Quality appraisal: Cochrane Risk of Bias 2.0

BIAS	AUTHOR'S JUDGMENT	SUPPORT FOR JUDGMENT
Randomization	Low	Quote "Randomisation was facilitated by a computer-generated random sequence using an interactive web-response system" "Interventions were packaged in identical bottles containing tablets of either 2mg Baricitinib or matching placebo"
Deviation from intervention	Low	Quote "Participants, study staff, and investigators were masked to the study assignment" Data analysis was done using intention-to-treat analysis which is appropriate.
Missing outcome data	Some concern	Considerable number of participants discontinued during the 28 day period of the study. Reported in the trial and shown in their prisma diagram. Baricitinib: 20 lost to follow up, 12 withdrew, 3 adverse events. Placebo: 22 lost to follow-up, 7 withdrew, 5 adverse events Although there is missing data, it is in approximately the same number in both treatment and placebo group. Differential discontinuation is due to different mortality outcomes. Some concern for 28-days all-cause mortality and 60-days all-cause mortality.
Measurement outcome	Low	Method of measurement outcome probably appropriate but measurement tools are not mentioned. Outcome assessors blinded for mortality and thrombolytic events For outcome "Progression to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation (including ECMO),or death, by day 28" and all-cause mortality, knowledge of intervention assignment cannot influence this outcome hence **Low Risk of Bias**
Selective reporting	Low	Comment: The protocol, statistical analysis plan and registries were available. Trial analyzed as pre-specified. Protocol deviations were in both the baricitinib and placebo group "(13.9% [106/764], baricitinib plus SOC and 12.9% [98/761], placebo plus SOC])" these did not affect the analyses and reporting of the results. Risk assessed to be low for the outcomes
Overall risk	Low	

Table 4. Characteristics of planned and ongoing studies (source: www.covid-nma.com 20 September 2021)

	Treatment (per arm)	Sample size	Severity at enrollment	Sponsor/Funder	Reg. number
1	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + baricitinib vs (3) Hydroxychloroquine + tocilizumab vs (4) Hydroxychloroquine + sarilumab vs (5) Hydroxychloroquine + siltuximab vs (6) Hydroxychloroquine + canakinumab vs (7) Hydroxychloroquine + methylprednisolone	1400	Moderate/severe	SOCIETA' ITALIANA MALATTIE INFETTIVE E TROPICALI	EUCTR2020-001854-23-IT
2	(1) Baricitinib vs (2) Placebo	35	Moderate/severe/critical	N/A	JPRN-jRCT2031200035
3	(1) Imatinib vs (2) Baricitinib vs (3) Standard of care	165	Moderate	Hospital Universitario de Fuenlabrada	NCT04346147
4	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Convalescent plasma treatment vs (4) Tocilizumab vs (5) Other corticosteroids vs (6) Azithromycin vs (7) Immunoglobulin vs (8) Casirivimab + imdevimab vs (9) Aspirin vs (10) Colchicine vs (11) Baricitinib vs (12) Anakinra vs (13) Dimethyl fumarate vs (14) Infliximab vs (15) Dexamethasone vs (16) Standard of care	40000	Moderate/severe/critical	University of Oxford	NCT04381936
5	(1) Baricitinib vs (2) Ravulizumab vs (3) Standard of care	1167	Moderate	Cambridge University Hospitals NHS Foundation Trust	NCT04390464
6	(1) Baricitinib vs (2) Standard of care	126	Severe	Azienda Ospedaliero, Universitaria Pisana	NCT04393051
7	(1) Remdesivir vs (2) Remdesivir + baricitinib	1032	Moderate/severe/critical	National Institute of Allergy and Infectious Diseases (NIAID)	NCT04401579
8	(1) Baricitinib vs (2) Placebo	1400	Moderate/severe	Eli Lilly and Company	NCT04421027
9	(1) Remdesivir + baricitinib vs (2) Remdesivir + dexamethasone	1500	Moderate/severe	National Institute of Allergy and Infectious Diseases (NIAID)	NCT04640168
10	(1) Remdesivir + baricitinib vs (2) Remdesivir + tocilizumab	150	Severe/critical	M Abdur Rahim Medical College and Hospital	NCT04693026
11	(1) Baricitinib vs (2) Remdesivir vs (3) Remdesivir + baricitinib vs (4) Standard of care	4000	Moderate/severe	ASST Fatebenefratelli Sacco	NCT04832880
12	(1) Baricitinib + dexamethasone vs (2) Dexamethasone vs (3) Emtricitabine + tenofovir vs (4) Standard of care	2193	Mild/moderate	Instituto de InvestigaciÃ³n Hospital Universitario La Paz	NCT04890626
13	(1) Baricitinib vs (2) Placebo	1900	Moderate/severe	Oslo University Hospital	NCT04891133
14	(1) Remdesivir + baricitinib vs (2) Remdesivir + dexamethasone	382	Moderate/severe	Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders	NCT04970719
15	(1) Baricitinib vs (2) Placebo	2000	Moderate/severe/critical	OSLO UNIVERSITETSSYKEHUS HF	EUCTR2021-000541-41-IT
16	(1) Baricitinib vs (2) Placebo	2000	Moderate/severe	Oslo University Hospital	EUCTR2021-000541-41-PT

Appendix 1: Search strategy

Database: Cochrane COVID-19 Study Register (https://covid-19.cochrane.org/)
Search strategy: baricitinib or azetidines or sulfonamides or purines or pyrazoles or Olumiant
Filtered by*:* Study type – interventional; Study Aim – treatment and management; Study design – parallel/crossover; Intervention Assignment - randomised
Output: 15 studies with 32 references (16 duplicates)
Date: 7 September 2021

Database: LOVE Platform (https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?utm=aile)
Search strategy: (baricitinib OR azetidines OR sulfonamides OR purines OR pyrazoles OR olumiant)
Filtered by: Systematic reviews and Primary studies (RCTs and Pending)
Output: 33 studies (0 duplicates)
Date: 7 September 2021

Database: PubMed
Search strategy: see table below
Output: 62 studies (4 duplicates)
Date: 7 September 2021

Search	Query	Results
#3	Search: #1 AND #2 Filters: Meta-Analysis, Randomized Controlled Trial, Systematic Review	62
#2	Search: baricitinib OR azetidines OR sulfonamides OR purines OR pyrazoles OR olumiant Filters: Meta-Analysis, Randomized Controlled Trial, Systematic Review	25,281
#1	Search: Coronavirus[mh:noexp] OR coronavirus*[tiab] OR corona virus*[tiab] OR COVID-19[mh] OR covid-19[tiab] OR covid19[tiab] OR covid 2019[tiab] OR SARS-Cov-2[mh] OR SARS-CoV-2[tiab] OR SARS-CoV2[tiab] OR SARSCoV2[tiab] OR SARsCov-2[tiab] OR SARS-coronavirus*[tiab] OR severe acute respiratory syndrome coronavirus 2[nm] OR severe acute respiratory syndrome coronavirus 2[tiab] OR 2019-nCov[tiab] OR 2019nCov[tiab] OR nCov2019[tiab] OR nCOV-2019[tiab] OR hCOV*[tiab] OR n-cov[tiab] OR ncov*[tiab]	184,185

Database: Living mapping and living systematic review of Covid-19 studies (www.covid-nma.com)
Reviewed ongoing trials and living SR data, https://covid-nma.com/networks/
Output: 16 ongoing studies
Date: **20 September 2021**

Appendix 2: Evidence to decision framework

Desirable Effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small **X Moderate** ○ Large ○ Varies ○ Don't know	See table below	The Committee raised concerns about the biological plausibility of the effect on mortality, given that no other outcomes were significantly different between baricitinib and placebo. However, the committee noted that the COV-BARRIER trial, was well conducted and reported. The excluded study that compared baricitinib plus remdesivir and remdesivir showed that baricitinib was associated with a reduction in mortality, although this was not significant.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
				Difference	
Mortality follow-up: 28 days № of participants: 1525 (1 RCT)	**HR 0.57** (0.41 to 0.78)	13.1%	**7.7%** (5.6 to 10.4)	**5.4% fewer** (7.5 fewer to 2.7 fewer)	⨁⨁⨁◯ Moderate[a]
Progression to mechanical ventilation or requiring oxygen № of participants: 1525 (1 RCT)	**HR 0.89** (0.74 to 1.06)	33.2%	**30.2%** (25.8 to 34.8)	**3.0% fewer** (7.4 fewer to 1.6 more)	⨁⨁⨁◯ Moderate[b]
Duration of ventilatory support № of participants: 1525 (1 RCT)	-	The mean days of supplemental oxygen use was **0**	-	mean **0.23 lower** (0.68 lower to 0.21 higher)	⨁⨁⨁⨁ High
Duration of ICU stay № of participants: 1525 (1 RCT)	-	The mean duration of ICU stay was **0** Days	-	mean **0.02 Days higher** (0.62 lower to 0.65 higher)	⨁⨁⨁⨁ High
Progression to ICU admission - not reported	-	-	-	-	-
Clinical outcome on ordinal scale follow-up: 28 days № of participants: 1525 (1 RCT)	**RR 1.00** (0.95 to 1.05)	77.8%	**77.8%** (73.9 to 81.7)	**0.0% fewer** (3.9 fewer to 3.9 more)	⨁⨁⨁⨁ High
Adverse events № of participants: 1525 (1 RCT)	**RR 1.00** (0.89 to 1.12)	43.9%	**43.9%** (39.1 to 49.2)	**0.0% fewer** (4.8 fewer to 5.3 more)	⨁⨁⨁⨁ High
Serious adverse events № of participants: 1525 (1 RCT)	**RR 0.81** (0.64 to 1.02)	17.7%	**14.4%** (11.4 to 18.1)	**3.4% fewer** (6.4 fewer to 0.4 more)	⨁⨁⨁◯ Moderate[b]
Adverse effects - not reported	-	-	-	-	-

	Deaths occurred in 62/764 (8.1%) in the baricitinib group and100/761 (13.1%) in the placebo (HR 0.57; 95% CI 0.41 to 0.78) resulting in 54 fewer deaths per 1000 people given the active treatment (from 75 fewer to 27 fewer).	
Undesirable Effects		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate **X Small** ○ Trivial ○ Varies ○ Don't know	See figure above. There was no difference in the number of adverse events between the baricitinib group (334/764; 43.7%) compared to placebo (334/761; 43.9%; RR 1.00; 95% CI 0.89 to 1.12).	
Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very ○ Low **x Moderate** ○ High ○ No included studies	There is overall moderate certainty evidence for the outcomes of interest. High certainty for days of supplemental oxygen use, progression to ICU admission, clinical improvement >2 points on NIAID-OS scale and adverse events. Moderate certainty for mortality, clinical deterioration - one category increase on NIAID-OS and SAEs.	The Committee was concerned that the evidence of benefit was limited to single study, and the primary outcome of the study was not significantly different between baricitinib and placebo. Mortality was one of several secondary endpoints (which were not adjusted for multiplicity), and was the only significant study finding. Usually secondary endpoints are considered hypothesis generating, and should be confirmed in further studies. Following GRADE guidance for assessing imprecision[1], the optimal sample size for the outcome mortality was calculated and it was found that the trial was slightly underpowered (taking into account loss to follow up of 20 participants in each group). Although corticosteroids were recommended by the committee as a therapeutic agent (essential medicine), based on a single, large RCT, the RECOVERY trial was a large (n=1844), non-industry-sponsored trial.

[1] "When assessing imprecision, one can calculate the number of patients required for an adequately powered individual trial (termed the ''optimal information size'' [OIS])": *Reference:* Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence-imprecision. J Clin Epidemiol. 2011;64(12):1283-93.

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **X Probably no important uncertainty or variability** ○ No important uncertainty or variability		Despite the lack of research evidence from stakeholders, the benefit of survival is likely to be considered of value.
Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison **X Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	The Committee considered that the balance of effects probably favours the intervention.	
Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
X Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Baricitinib: estimated budget impact** • **Cost per patient for 14 days**: (Single exit price) R4220 • **COV-BARRIER inclusion criteria** - Age ≥18 years - Raised inflammatory marker (CRP, LDH, ferritin) - Not on invasive mechanical ventilation - Protocol amended during study to include only those on oxygen	The Committee considered the direct medicine price of baricitinib, noting that baricitinib may be administered orally and via the nasogastric tube. Assumptions for the model: • Patients eligible for baricitinib if they require oxygen, and have at least one raised inflammatory marker • Single exit prices used • Baricitinib would be readily available (currently SAHPRA registered)

DATCOV data, public sector hospitals *(patient numbers)*:

	Wave 1	Wave 2	Wave 3
Total admissions	39904	65210	84993
On oxygen	16994	26789	40709
Ventilated	3867	5458	8897

Reporting improved between Wave 1 and 2. By Wave 3, includes data from all public sector hospitals in SA.

- **Proportion of SARS-CoV2 patients with raised CRP:** 40% used in tocilizumab review (WC data). Likely to be higher in subgroup on oxygen: assumed 80%.
- Potential impact of vaccinations on hospital admissions and disease severity not taken into account.

Budget impact (Rands) ranges based on above assumptions

	Wave 3	20% lower	20% higher
Patients on oxygen with raised CRP (40%)	16 000	12 800	19 200
Budget impact range	**R 67 520 000**	**R 54 016 000**	**R 80 640 000**
Patients on oxygen with raised CRP (80%)	32 000	25 600	38 400
Budget impact range	**R 135 040 000**	**R 108 032 000**	**R 162 048 000**

The estimated ICER for baricitininb was calculated as R6 252 per life year saved.

Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	There are no included studies on this.	

Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced **X Probably reduced** ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence is available.	The Committee considered that affordability would probably impact equity. National Treasury funding would reduce inequitable access across provinces. Supply constraints would also result in inequitable access.
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no **X Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence is available.	The committee considered that given the potential benefit, this medicine would be acceptable to most stakeholders affected by this intervention (healthcare providers and patients).

Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies **X Don't know**	Baricitinib is SAHPRA registered (in combination with remdesivir) to treat COVID-19 in those who require supplemental oxygen. Although the originator branded remdesivir has also been registered by SAHPRA, access is currently dependent on generic remdesivir, imported as section 21 medicine. Medicine availability: the product is not listed on the EML and is not available on tender in the public sector. Use of the medicine does not require special training for use as it can be given orally or via a nasogastric tube.	Single supplier to satisfy global demand is a concern. Baricitinib was first registered in South Africa in January 2021 and is available only from the single source (Eli Lilly SA (Pty) Ltd). There are concerns about the volumes that would be accessible, in the light of increasing global demand. Shortages have already been reported in high-income countries (https://www.pharmacytimes.com/view/newest-covid-19-surge-leads-to-shortages-in-therapeutics; https://www.healio.com/news/rheumatology/20210916/cascade-of-impact-covid19-surge-again-threatens-patient-access-to-maintenance-drugs). Eli Lilly has already licensed a number of Indian generic versions (https://investor.lilly.com/news-releases/news-release-details/lilly-accelerating-baricitinibs-availability-india-following; https://www.business-standard.com/article/companies/eli-lilly-signs-licensing-pact-with-cipla-sun-lupin-for-covid-19-drug-121051100039_1.html). However, access to generic versions will require either section 21 approval or registration by the generic firms involved (Sun Pharma, Cipla, Lupin).

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	15 October 2021	MB, RdW, TK, VN, NB	Baricitinib recommended for use in hospitalised COVID-19 patients on oxygen and who have at least one raised inflammatory marker on specialist motivation/ consultation. This recommendation is conditional on baricitinib being accessible to all eligible public sector patients in South Africa. Baricitinib reduced mortality in a single study, and was not associated with an increased risk of adverse events; cheaper than tocilizumab, and may be administered orally (or via nasogastric tube).
Second	19 November 2021	MB, RdW, TK, VN, NB	Recommendation updated without the need for specialist motivation/ consultation, as patients would be treated at secondary level facilities. Basic incremental cost-effectiveness ratio included.