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

TITLE: COLCHICINE FOR COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 12 February 2021 *(second update of original 6 August 2020 rapid review report)*

Key findings

- We conducted a rapid review of available clinical evidence regarding the efficacy and safety of colchicine treatment in patients with COVID-19, regardless of whether they require hospitalisation. This is an expansion of the original PICO, which examined the efficacy and safety of colchicine in hospitalised patients only.
- A comprehensive search on 28 January 2021 identified nine published reports (relating to four randomised controlled trials and one systematic review), as well as 25 planned or ongoing studies.
- The four randomised controlled trials included a total of 248 hospitalised patients and 4 488 non-hospitalised patients aged ≥40 years with at least one high-risk criterion. One trial reached its intended sample size, two trials did not reach their planned sample size; it is unclear whether the fourth reached its planned sample size.
- The effect of colchicine on all-cause mortality is uncertain in both hospitalised (OR 0.21; 95% CI 0.03 to 1.28; 2 RCTs; very low certainty evidence) and non-hospitalised (OR 0.56, 95% CI 0.19 to 1.67; 1 RCT; very low certainty evidence) COVID-19 patients.
- The effect of colchicine on progression to mechanical ventilation in hospitalised patients is uncertain. In non-hospitalised patients, colchicine may reduce progression to mechanical ventilation, but this was not statistically significant (OR 0.53, 95% CI 0.25 to 1.09; 1 RCT; low certainty evidence).
- Colchicine may reduce hospitalisation in previously non-hospitalised patients with PCR-confirmed or clinically suspected COVID-19 (OR 0.79; 95% CI 0.60 to 1.03; 1 RCT; low certainty evidence). In the same RCT, restricting to PCR-confirmed cases only, the reduction in hospitalisation was similar (OR 0.75; 95% CI 0.57 to 0.99; low certainty evidence). NNT to prevent one hospitalisation in PCR-confirmed cases is 72.
- The extent to which colchicine use is associated with serious adverse events (SAEs) and adverse events (AEs) in hospitalised patients is uncertain. In non-hospitalised patients, colchicine is associated with a lower incidence of SAEs, when compared to placebo, but this was not statistically significant (OR 0.77; 95% CI 0.59 to 1.09; 1 RCT; low certainty evidence), but is associated with more AEs when compared to placebo (OR 1.78; 95% CI 1.50 to 2.00; 1 RCT; moderate certainty evidence). In the pooled analysis including hospitalised and non-hospitalised patients, similar results were found.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE 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 Sub-committee suggests not to use colchicine for the treatment of COVID-19 in hospitalised and non-hospitalised patients, unless in the context of an approved clinical trial.

Rationale: The evidence of efficacy and safety is uncertain at this point, with insufficient evidence of clinically relevant benefits, an increased risk of adverse effects, and an uncertain risk of serious adverse effects.

Level of Evidence: Very low to low certainty evidence

Review indicator: Evidence of safety and/or efficacy that is sufficient to change the recommendation.

Note: Consensus was not reached amongst Committee members, but most would likely not recommend the intervention.

(Refer to appendix 5 for the evidence to decision framework)

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish *(Chair)*, Helen Rees, Gary Reubenson *(Vice-Chair)*.

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

BACKGROUND

Colchicine, an oral anti-inflammatory drug used to treat gout, has been proposed as a potential treatment for COVID-19. Its mechanisms of action include inhibition of neutrophil and monocyte recruitment, and inhibition of pro-inflammatory cytokines, both of which are thought to be important mediators of COVID-19 disease severity.[1,2]

This update of the rapid review was triggered by the publication of the COLCORONA study results by Tardif *et al.* (2020)[3], in pre-print form.

RESEARCH QUESTION: Should colchicine be used for managing patients with COVID-19, with or without other medicines?

METHODS

We conducted a rapid review of the evidence relating to colchicine through the systematic searching of three electronic databases (Epistemonikos, the Cochrane COVID Register and www.covid-nma.com) on 17 July 2020, and updated the search on 7 October 2020 and 28 January 2021. The search strategy is shown in Appendix 1. Screening of records was done independently and in duplicate (MM and AB for the updates), with arbitration by a third reviewer where necessary, using Covidence systematic review software.

For living systematic reviews of RCTs on www.covid-nma.com, the quality of randomised controlled trials was assessed[4] using the Risk of Bias 2 (RoB 2) tool.[5] The trial for which methodological rigour had not yet been assessed by the covid-nma authors was appraised, using RoB 2, by AB and checked by MM. Where possible, data from different trials were pooled in a meta-analysis, using Review Manager 5 software[6], by MM and checked by AB. Evidence profiles were also generated for www.covid-nma.com and by the review team using GRADEPro software[7], with all ordinal scale outcomes transformed to the WHO 10-point ordinal scale[8] for the purposes of standardisation (Appendix 3). A score of 6 corresponded with requiring oxygen by non-invasive ventilation (NIV) or high flow nasal cannulae (HFNO); 7 with intubation and mechanical ventilation; 8 with mechanical ventilation or vasopressors; 9 with mechanical ventilation and vasopressors, dialysis, or extracorporeal membrane oxygenation (ECMO); and 10 with death.

MAGICapp[9], using GRADE methodology, was also consulted as a living ecosystem of evidence from the Australian guidelines for the clinical care of people with COVID-19. Where the same information was available in a published systematic review as well as a living ecosystem of evidence, the authors used living systematic reviews preferentially for updating treatment effects, where appropriate. Relevant study data were extracted in a narrative table of results (MM for the update); results were reviewed, checked and reported by another reviewer (AB). RdW and AG reviewed the overall report.

Eligibility criteria for review

Population: Patients with confirmed COVID-19, no restriction to age or co-morbidity.

Intervention: Colchicine, 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 or active comparator).

Outcomes: Mortality; hospitalisation; duration of hospitalisation; proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis; time to negative SARS-CoV-2 PCR on nasopharyngeal swab; progression to ICU admission; progression to mechanical ventilation; progression to requiring oxygen; duration of ICU stay; adverse reactions and adverse events; clinical improvement on an ordinal scale at chosen time points; and time to clinical improvement.

Study designs: Systematic reviews of randomised controlled trials; individual randomised controlled trials.

RESULTS

Results of search

After the removal of 215 duplicates, two reviewers screened 100 records and identified four randomised controlled trials[3,10-12]. One systematic review by Han et al 2021[13] was also identified, but the review comprised the results of two previously included trials[10,11] which had already been synthesised by MAGICapp[9]. See Figure 1 for the PRISMA flow diagram.

A total of 25 ongoing trials were identified among the 35 eligible full-text records. Table 1 shows the main characteristics and outcomes of the included trials, Table 2 describes the excluded studies and Table 3 summarises the ongoing trials.

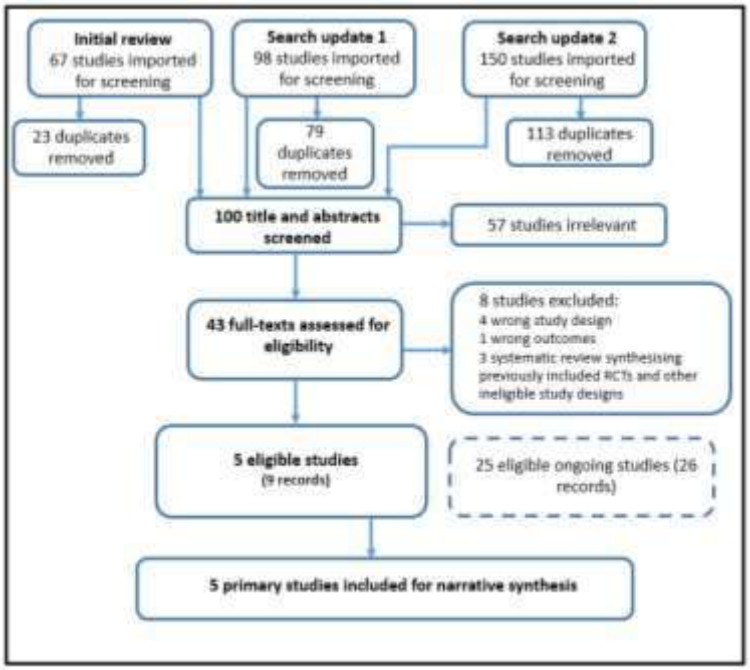

Figure 1. PRISMA flow diagram for review

Description of included studies

We found four randomised controlled trials, conducted in Greece, Brazil, Iran, Canada, USA, South Africa, and unspecified countries in Europe and South America, which included a total of 4 736 patients, of which 248 were hospitalised patients with confirmed COVID-19 (with moderate to critical severity) and 4 488 were non-hospitalised patients with COVID-19. Tardif *et al.* (2021)[3] randomised 4 488 non-hospitalised adult patients aged ≥40 years with COVID and at least one 'high-risk' criterion to treatment with colchicine or placebo. This is the largest trial to date, but has yet to be published in peer-reviewed form. In addition, the trial was terminated early due to logistical issues, and consequently did not reach the planned sample size of 6 000.

The RCT by Deftereos *et al.* (2020)[10] initially aimed to recruit 180 patients (which would provide 90% power to detect a 50% reduction in the primary clinical end point: time to a 2-point deterioration on a 7-point modified ordinal scale, at α=0.05), but only included 110 patients due to declining incidence of COVID-19 in Greece. The 7-point modified ordinal scale used by the authors of the trial is shown in Appendix 2. The authors reported that the trial was not powered to detect differences in rare adverse events. Of note, the vast majority of the included patients received concomitant treatment thought at the time to have an effect on SARS-CoV-2, mostly chloroquine or hydroxychloroquine (98%) and azithromycin (92%). Lopes *et al.* (2021)[11] reported on a study that achieved the target sample size (n=30 per trial arm). The primary endpoints were clinical parameters, such as the time of need for supplemental oxygen; time of hospitalisation; need for admission and length of stay in ICU; and death rate and causes of mortality. Salehzadeh *et al.* (2020)[12] included 100 patients and the planned outcomes included duration of

hospitalisation; cessation of fever; mortality; transfer to ICU and discharge. However, the authors only reported duration of hospitalisation and inflammatory biomarkers.

Effects of the intervention

The currently available evidence on the safety and effectiveness of colchicine for the treatment of people with COVID-19 requiring hospitalisation is of low certainty. However, the certainty of evidence has improved since earlier reviews in 2020; evolving from very low to low certainty.

The evidence profiles for results in non-hospitalised patients are presented in Table 4.1; evidence profiles for the pooled evidence from both hospitalised and non-hospitalised patients are found in Table 4.2. Certainty of evidence for hospitalised patients, updated from covid-nma to reflect the publication of Lopes *et al.* (2021)[11], is reported narratively in text. The quality appraisal of two RCTs[10,12], taken from www.covid-nma.com, can be found in Tables 5.1 and 5.3; the quality appraisal of the remaining two RCTs[3,11], done or updated by the review team, can be found in Table 5.2 and 5.4.

All-cause mortality

Three RCTs assessed all-cause mortality: two included RCTs[3,10] were not powered to detect a difference in mortality; while a third reached its intended sample size[11]. A meta-analysis (Figure 2) of the studies in hospitalised patients found no significant difference in mortality at day 14 to day 28 (OR 0.21; 95% CI 0.03 to 1.28; 2 RCTs; very low certainty evidence due to serious risk of bias and very serious imprecision).

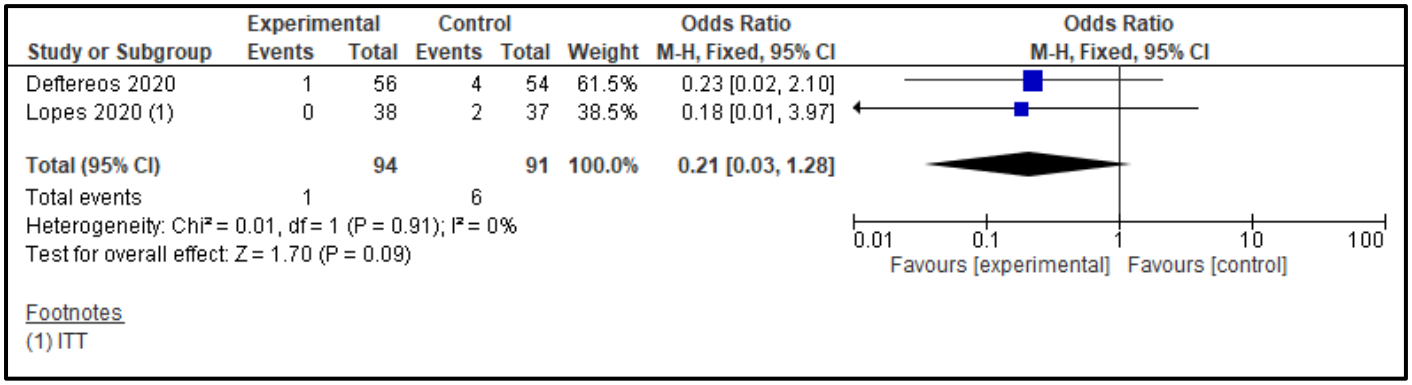

Figure 2. Forest plot for all-cause mortality in hospitalised patients with COVID-19

The findings were similar for non-hospitalised patients (OR 0.56; 95% CI 0.19 to 1.67; 1 RCT; very low certainty evidence) and for both hospitalised and non-hospitalised patients, combined (OR 0.41; 95% CI 0.16 to 1.03; 3 RCTs; low certainty of evidence). See Figure 3 for the pooled results for all-cause mortality from the combined analysis.

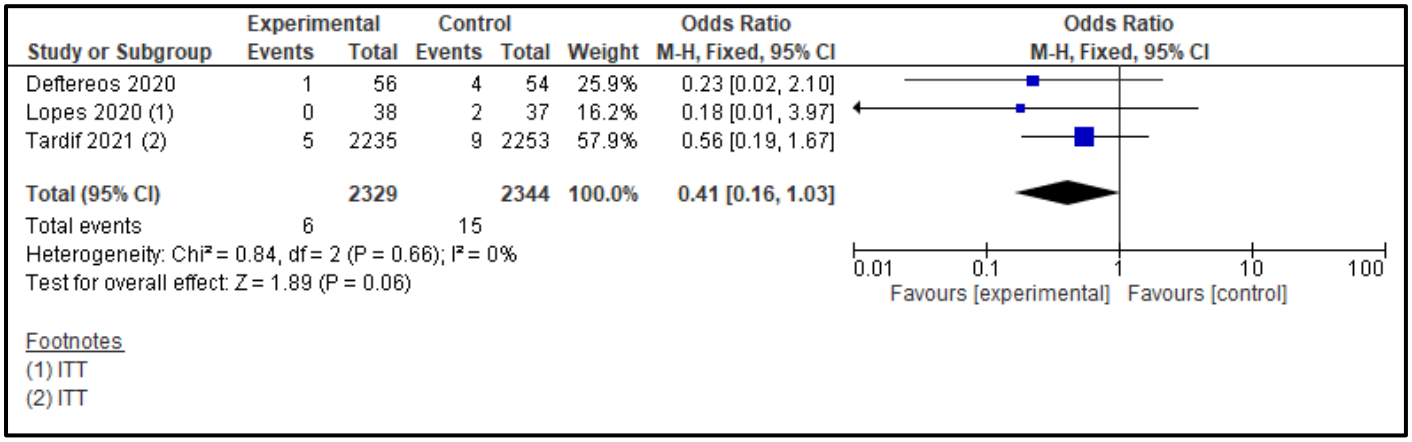

Figure 3. Forest plot for all-cause mortality in hospitalised and non-hospitalised patients with COVID-19

Hospitalisation

Available evidence indicates that colchicine may reduce the need for hospitalisation in previously non-hospitalised patients with COVID-19. Tardif *et al.* (2021)[12] reported a reduced odds of hospitalisation (OR 0.79; 95% CI 0.60 to 1.03) in the intention-to-treat analysis (including both PCR-confirmed and clinically suspected COVID-19), and in the per protocol analysis (PCR-confirmed COVID-19 only) (OR 0.75; 95% CI 0.57 to 0.99). This is assessed as low certainty evidence (Table 4.1).

Duration of hospitalisation

Deftereos *et al.* (2020)[10] reported the median (IQR) duration of hospitalisation to be 12 days (9 to 22) in the colchicine group and 13 days (9 to 18) in the control group, with no significant difference between the two groups (p=0.91). Lopes *et al.* (2021)[11] reported a median (IQR) of 9 days (7 to 12) in the control group to 7 days (5 to 9) in the colchicine group. Similarly Salehzadeh *et al.* (2020)[12] reported a mean of 8.12 days in the placebo group and 6.28 days in the colchicine group; assessed as very low certainty evidence due to very serious risk of bias and very serious imprecision[9].

Proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab

None of the included studies reported on this outcome.

Time to negative SARS-CoV-2 PCR on nasopharyngeal swab

None of the included studies reported on this outcome.

Progression to ICU admission

Lopes *et al.* (2021)[11] reported progression of hospitalised patients to ICU admission for 2/38 (5%) participants in the colchicine and 4/37 (11%) participants in the control group (OR 0.46; 95% CI 0.08 to 2.67; 1 RCT; very low certainty of evidence due to serious risk of bias and very serious imprecision).

Progression to mechanical ventilation or incidence of WHO 10-point scale progression score ≥ 7

We are very uncertain whether colchicine has an effect on the incidence of progression to mechanical ventilation in hospitalised patients. In the RCT by Deftereos[10], a total of 1/56 patients in the colchicine group and 6/54 in the control group progressed to a 10-point WHO score of 7 or above (where 7 is mechanical ventilation; 8 is mechanical ventilation or vasopressors; 9 is mechanical ventilation and vasopressors, dialysis, or ECMO; and 10 is death) at day 14 to day 28 (RR 0.16; 95% CI 0.02 to 1.29; very low certainty evidence)[4].

We are uncertain whether colchicine has an effect on the incidence of progression to mechanical ventilation in non-hospitalised patients, with Tardif *et al.* (2021)[3] reporting on the proportion requiring mechanical ventilation (OR 0.53; 95% CI 0.25 to 1.09; 1 RCT; low certainty evidence).

Progression to requiring oxygen by non-invasive ventilation (NIV) or high-flow nasal oxygen (HFNO) (incidence of WHO 10-point scale progression score ≥ 6)

Lopes *et al.* (2021)[11] reported a highly significant reduction in the median (IQR) time of supplemental oxygen provision, from 6.5 (4 to 9) days in the control group to 4 (2 to 6) days in the colchicine group (p=0.02).

Duration of ICU stay

Lopes *et al.* (2021)[11] reported no difference in duration of ICU stay, but 4 patients in the control group and 2 patients in the colchicine group required ICU admission. The durations of ICU stay were 11 days for the control patients and 12 days for the patients treated with colchicine.

Serious adverse events (SAEs)

The available evidence is very uncertain regarding the effect of colchicine on SAEs in hospitalised patients. Two out of 75 (3%) patients in the colchicine group and 2/73 (3%) patients in the control group experienced a serious adverse event when pooling the results of RCTs by Deftereos *et al.* (2020)[10] and Lopes *et al.* (2021)[11] (OR 0.97; 95% CI 0.13 to 7.29; 2 RCTs; very low certainty evidence due to serious risk of bias and very serious imprecision). See Figure 4 for the pooled results of SAEs in hospitalised patients.

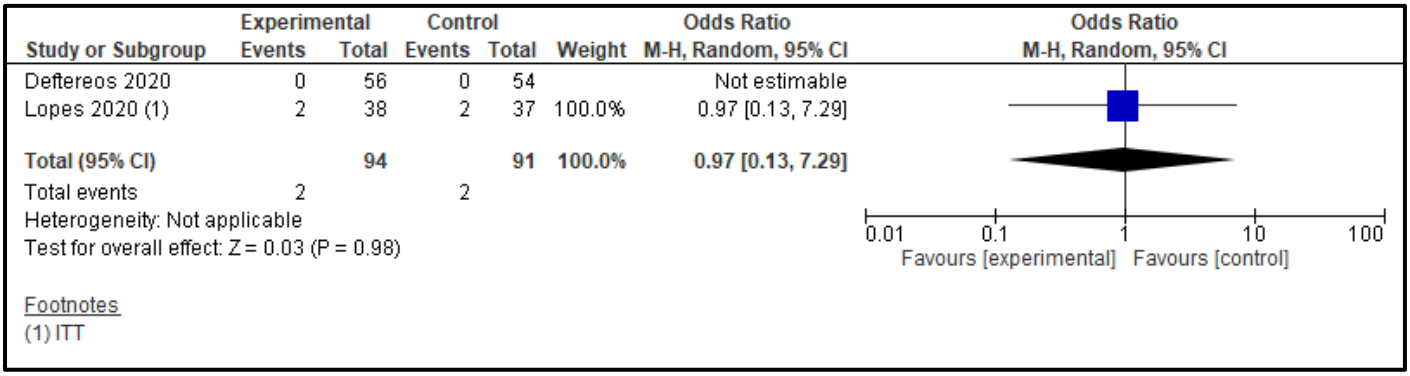

Figure 4. Forest plot for serious adverse events in hospitalised patients with COVID-19

In non-hospitalised patients, more SAEs were reported in the control than the treatment arm (OR 0.77; 95% CI 0.59 to 1.09; 1 RCT; low certainty evidence). Pneumonia comprised 155/247 (63%) of SAEs in total. Given the dominant weight from this large RCT (Tardif *et al.* (2021)[3]), the pooled estimate for non-hospitalised and hospitalised patients was similar (OR 0.78; 95% CI 0.60 to 1.00; 3 RCTs; low certainty evidence). See Figure 5 for the pooled results for serious adverse events from the combined analysis.

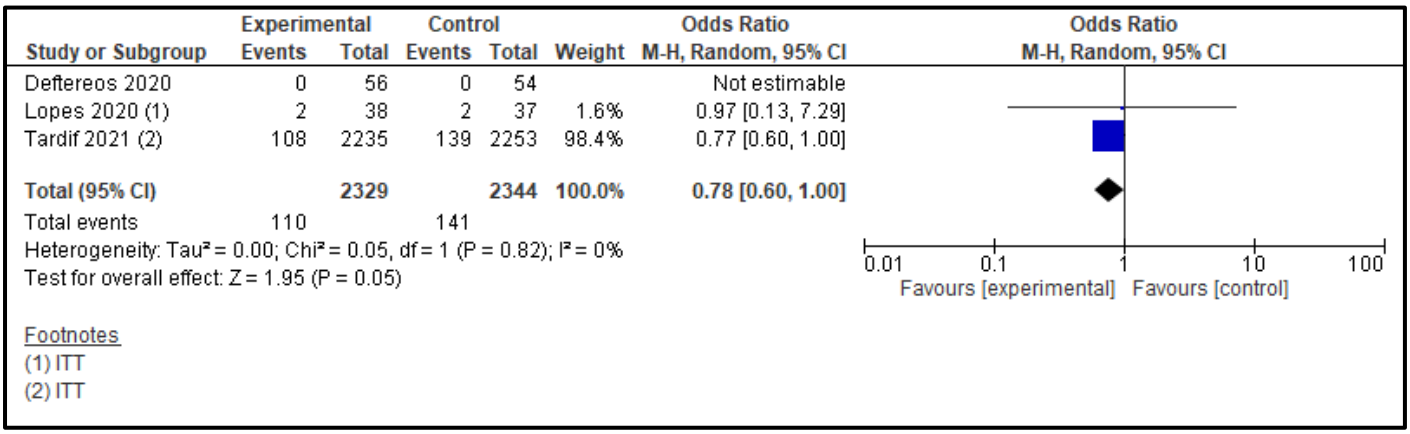

Figure 5. Forest plot for serious adverse events in hospitalised and non-hospitalised patients with COVID-19

Adverse reactions and adverse events (AEs)

The available evidence is very uncertain regarding the risk of AEs with colchicine in hospitalised patients. In the RCT by Deftereos *et al.* (2020)[10], 43/55 (78%) patients in the colchicine and 15/50 (30%) in the control group experienced adverse events (RR 2.61; 95% CI 1.67 to 4.07; 1 RCT; very low certainty evidence)[9]. The RCT by Lopes *et al.* (2021)[11] reported AEs in 10/38 (26%) patients in the intervention group and 8/37 (22%) patients in the control group (OR 1.29; 95% CI 0.39 to 4.36; 1 RCT; very low certainty evidence due to serious risk of bias and very serious imprecision).

In the RCT by Deftereos *et al.* (2020)[10], the most frequently reported adverse events in both groups was diarrhoea (significantly higher in intervention group: 45.5% vs 18%; p=0.003), with vomiting, nausea, and headache also reported in both groups. The aforementioned are all expected adverse effects associated with colchicine, when used at therapeutic doses for acute gout. Other adverse events in the control group were acute renal failure, pancytopenia, and thrombophlebitis; the intervention group reported one event thought to have been caused by colchicine (elevated liver enzymes, reversed following cessation) and five with uncertain relation to colchicine (elevated liver enzymes, rhinorrhagia, allergic reaction, cutaneous rash and chest discomfort).

Additionally, in the intervention group, two patients had to stop study drugs due to diarrhoea, five had abdominal pain and one developed muscle spasms. One patient per group (1.8% in intervention and 2.0% in control) developed an adverse event judged by field investigators as serious (one case each of thrombocytopenia and diarrhoea), but neither met the RCT's protocol definition of serious according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute (i.e. noninvasive intervention indicated). These adverse events were consequently rated as moderate severity.

In non-hospitalised patients, the use of colchicine increased the odds of experiencing an AE (OR 1.78; 95% CI 1.50 to 2.00; 1 RCT; moderate certainty evidence). A combined analysis of hospitalised and non-hospitalised patients also showed an increased risk of experiencing an AE in patients receiving colchicine compared with placebo (OR 1.72; 95% CI 1.49 to 2.00; 2 RCTs; moderate certainty evidence), as shown in Figure 6.

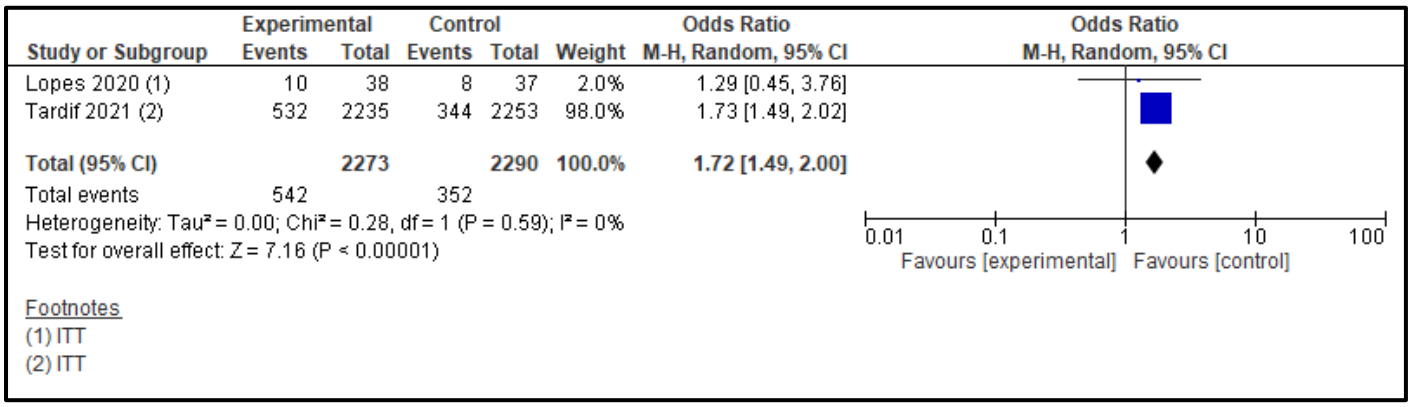

Figure 6. Forest plot for any adverse events in hospitalised and non-hospitalised patients with COVID-19

Other reported outcomes (not pre-specified for this review)

In the non-hospitalised population, Tardif *et al.* (2021)[3] reports a primary composite endpoint consisting of mortality and number of hospitalisations for COVID-19, with similar results by ITT (OR 0.79; 95% CI 0.61 to 1.03) and per protocol analysis (OR 0.75; 95% CI 0.57 to 0.99).

The primary endpoints reported by Deftereos *et al.* (2020)[10] were surrogates based on laboratory values (maximum high-sensitivity cardiac troponin level and the time for C-reactive protein to reach more than 3 times the upper reference limit) and the time to deterioration by 2 points on the 7-grade WHO clinical status scale. The median (IQR) peak high-sensitivity cardiac troponin values were 0.0112 (0.0043 to 0.0093) ng/mL in the control group and 0.008 (0.004 to 0.0135) ng/mL in the colchicine group (p = 0.34). Median (IQR) maximum C-reactive protein levels were 4.5 (1.4 to 8.9) mg/dL vs 3.1 (0.8 to 9.8) mg/dL (p = 0.73), respectively. The mean (SD) duration to clinical deterioration of 2 points on a 7-grade[i] clinical status scale (based on the World Health Organization R&D Blueprint Ordinal Clinical Scale) was 20.7 (0.31) days in the intervention group and 18.6 (0.83) days in the control group. The cumulative event-free (2-point clinical deterioration) 10-day survival was significantly higher for the intervention: 97% in the colchicine group and 83% in the control group (Gehan statistic, 4.9; P=0.03).

CONCLUSION

The current evidence does not support the inclusion of colchicine in treatment guidelines for hospitalised and non-hospitalised COVID-19 patients in South Africa. Additional trials may inform this evidence base further.

Reviewers: Updated review: Michael McCaul, Amanda Brand, Renee de Waal, Andy Gray.

Declaration of interests: MM (Centre for Evidence-based Health Care, Stellenbosch University and SA GRADE Network), AB (Centre for Evidence-based Health Care, Stellenbosch University and SA GRADE Network), RdW (School of Public Health and Family Medicine, University of Cape Town) and AG (Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal) have no relevant conflicts of interest to declare.

[i] Note that the study reported on the 7-grade ordinal scale (Appendix 3), but the GRADE assessment by Bollig et al. converted these scores to a 10-grade ordinal scale (Appendix 4) to enable comparison with other publications.

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Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Main findings
Tardif, J-C *et al.* medRxiv 2021[3] Pre-print	Double-blind, randomized controlled trial Multicentre (across 6 countries) Trial was terminated early (75% of planned study participants enrolled and completed 30 day follow up) due to logistical issues.	Setting: Multicentre trial across 6 countries (Canada, USA, South Africa; and unspecified countries in Europe and South America) n= 2235 (Colchicine) n= 2253 (Placebo) Age, mean (sd): 54,4 (9,7) intervention arm; 54,9 (9,9) control arm Gender, Female, n (%): 1238 (55,4) intervention arm; 1183 (52,5) control arm BMI, mean (sd): 30 (6,2) intervention arm; 30 (6,3) control arm Comorbidities (% intervention; % control): Smoking (9,7; 9,4), Hypertension (34,9; 37,6), DM (19,9; 20), Respiratory disease (26,1; 26,9), Prior MI (2,9; 3,2), Prior heart failure (1,1; 0,8). Eligibility: **Non-hospitalised** adult patients (>40 years) with COVID within 24hrs of enrollment, presenting with one of the following: age of 70 years or older, obesity (body-mass index of 30 kg/m2 or more), diabetes, uncontrolled hypertension (systolic blood pressure ≥150 mm Hg), known respiratory disease, known heart failure, known coronary disease, fever of at least 38.4°C within the last 48 hours, dyspnea at the time of presentation, bicytopenia, pancytopenia, or the combination of high neutrophil and low lymphocyte counts.	**Intervention** Colchicine 0.5mg twice daily for first 3 days and once daily thereafter for 27 days **Control** Placebo for 30 days (oral tablets) Mean treatment duration for trial medication was 26,2 days.	**<u>ITT population (n=4 488), OR (95% CI), n (%)</u>** **Mortality** OR 0,56 (0,19 to 1,67), 5 (0,2) intervention vs 9 (0,4) control **Primary composite endpoint (death or hospitalisation for COVID-19)** OR 0,79 (0,61 to 1,03), 104 (4,7) intervention vs 131 (5,8) control **Hospitalisation for COVID** OR 0,79 (0,6 to 1,03), 101 (4,5) intervention vs 128 (5,7) control **Mechanical ventilation** OR 0,53 (0,25 to 1,09), 11 (0,5) intervention vs 21 (0,9) control. **<u>Patients with PCR-proven COVID (n=4 159), OR (95% CI), n (%)</u>** **Mortality** OR 0,56 (0,19 to 1,66), 5 (0,2) intervention vs 9 (0,4) control **Primary composite endpoint** OR 0,75 (0,57 to 0,99), 96 (4,6) intervention vs 126 (6) control **Hospitalisation for COVID** OR 0,75 (0.57 to 0,99), 93 (4,5) intervention vs 123 (5,9) control **Duration of hospitisation** Not reported **Mechanical ventilation**

Citation	Study design	Population (n)	Treatment	Main findings
				OR 0,5 (0,23 to 1,07), 10 (0,5) intervention vs 20 (1) control **Adverse events/reactions (ITT*)** **Any SAE**, OR 0,77 (0.59 to 1,09), 108 (4,9) intervention vs 139 (6,3) control. **Any related AE**, OR 1,78 (1,5 to 2), 532 (24,2) intervention vs 344 (15,5) control **Pneumonia SAE**, OR 0,68 (0,48 to 0,95), 63 (2,9) intervention vs 92 (4,1) control **Pulmonary embolism**, OR 5,57 (1,2 to 51,8), 11 (0,5) intervention vs 2 (0,1) control **Gastro-intestinal SAE**, OR 2 (0,4 to 12,4), 6 (0,3) intervention vs 3 (0,1) control **Gastro-intestinal AE**, OR 1,7 (1,5 to 2), 524 (23,9) intervention vs 328 (14,8) control **Diarrhea AE**, OR 2 (1.6 to 2.4), 300 (13,7) intervention vs 161 (7.3) control **Nausea AE**, OR 0.92 (0.59 to 1.4), 43 (2) intervention vs 47 (2.1) control **GI haemorrhage AE**, OR not estimable, 1 (0) intervention vs 0 (0) control **Rash AE**, OR 0.3 (0.07 to 1), 4 (0,2) intervention vs 13 (0,6) control*Total randomized as denominator.
Deftereos, SG *et al.* JAMA 2020[10] Journal publication	Prospective, open-label, randomised clinical trial Multicenter (n=16 tertiary care hospitals) Trial was terminated early due to slow enrolment in Greece in late April 2020.	Setting: Greece (**in hospital**) n = 54 (Standard treatment) n = 56 (Colchicine, in addition to standard treatment) Severity: Mild: n=0 / Moderate: n=102/ Severe: n=3 Critical: n=0 Age, median (IQR): 65 (54-80) intervention; 63 (55-70) control Gender Male, n (%): 30 (60.0) intervention; 31 (56.4) control Eligibility: 1. Subjects ≥18 years old with laboratory confirmed SARS-CoV-2 PCR, who presented with	**Treatment** Colchicine (loading dose 1.5 mg; followed by 0.5 mg 60 minutes later if no adverse gastrointestinal effects; then 0.5 mg twice daily (reduced to once daily if body weight <60 kg) until hospital discharge or a maximum of 21 days.) Co-Intervention: Standard care Duration: 21 days **Control** Standard care: optimal medical	**In the report** The primary end points were the difference in maximal high-sensitivity cardiac troponin (hs cTn) levels, the time for C-reactive protein to reach levels > 3 times the upper reference limit, and the time from baseline to clinical deterioration, defined as a 2-grade increase on an ordinal clinical scale, based on the World Health Organization R&D Blueprint Ordinal Clinical Scale within a time frame of 3 weeks after randomisation or until hospital discharge (whichever occurred first). **All-cause mortality** Control: 4/54 (7.4%) vs intervention: 1/56 (1.8%).

Citation	Study design	Population (n)	Treatment	Main findings
		clinical symptoms including body temperature >37.5°C. AND 2. At least two of the following criteria: persistent cough, persistent throat pain, anosmia, ageusia, asthenia, arterial blood partial pressure of oxygen (PaO_2) <95 mmHg.	treatment according to local protocols, as established by the National Public Health Organization and following the guidance of the European Centre for Disease Prevention and Control Concomitant treatment: Most patients received chloroquine or hydroxychloroquine (103; 98.1%) and azithromycin (97; 92.4%). No patients were reported to have received corticosteroids.	**Duration of hospitalisation** Median (IQR) hospitalisation was 12 (9-22) days in the intervention and 13 (9-18) days in the control group (p=0.91). **The percentage of participants requiring mechanical ventilation, in those who deteriorated by at least 2 points on the ordinal scale (as defined by Deftereos et al.):** Control: 6/7 (85.7%), Intervention= 1/1 (100.0%). **Number, type, severity, and seriousness of adverse events.** Adverse events were similar for the two groups, with no significant differences by event. The exception was diarrhoea, which was more frequent in the colchicine group; 25/55 (45.5%) patients in the intervention and 9/50 (18.0%) patients in the control group (P=0.003) experienced this event. **Time to deterioration by 2 points on the 7-grade WHO clinical status scale** Control: Mean (SD) 18.6 (0.83) days vs Intervention: 20.7 (0.31) days. **Cumulative event-free 10-day survival** Control: 83% vs Intervention: 97%. **Maximum high-sensitivity cardiac troponin level** Control: Median (IQR) 0.0112 (0.0043-0.0093) vs Intervention: 0.008 (0.004-0.0135) ng/mL. **Maximum C-reactive protein level** Control: Median (IQR) 4.5 (1.4-8.9) mg/dL vs Intervention 3.1 (0.8-9.8) mg/dL.
Lopes, MIF *et al.* RMD Open 2021[11] Journal publication	RCT, double blind, placebo controlled	Setting: Brazil n=38 (Colchicine)	**Treatment** Colchicine (0.5mg thrice daily for 5 days, then 0.5mg twice daily for 5	**All-cause mortality** Control: 2/37 vs Intervention: 0/38

Citation	Study design	Population (n)	Treatment	Main findings
	Single centre 11 April to 30 August 2020	n=37 (Placebo) Age (years, median (IQR)): 54.5 (42.5 to 64.5) in intervention; 55 (42 to 67) in control 33 males (19 in intervention and 14 in control) Severity : Mild: n=0 / Moderate: n=12/ Severe: n=23 Critical: n=3 (severity from interim analysis) Comorbidities (% intervention; % control): Current or former smoking (19; 25), respiratory diseases (11; 14), cardiovascular diseases (47; 44), diabetes mellitus (36; 42), dyslipidemia (28; 33) Inclusion criteria: Individuals **hospitalised** with moderate or severe forms of COVID-19 diagnosed by RT-PCR in nasopharyngeal swab specimens and lung computed tomography scan involvement compatible with COVID-19 pneumonia; older than 18 years; body weight > 50 kg; normal levels of serum Ca2+ and K+; QT interval < 450 ms at 12 derivations electrocardiogram (according to the Bazett formula) and negative serum or urinary β-HCG if women under 50. Exclusion criteria: Mild form of COVID-19 or in need for ICU admission; diarrhea resulting in dehydration; known allergy to colchicine; diagnosis of porphyria, myasthenia gravis or uncontrolled arrhythmia at enrollment; pregnancy or lactation; metastatic cancer or immunosuppressive chemotherapy; regular use of digoxin, amiodarone, verapamil or protease inhibitors; chronic liver disease with hepatic failure; inability to understand consent form.	days) with loading dose of 1.0 mg if body weight was ≥ 80 kg Co-Intervention: Standard care as described for control Duration : 10 days **Control** Placebo Duration : 10 days All participants received the institutional treatment for COVID-19 with azithromycin 500 mg once daily for up to 7 days, hydroxychloroquine 400 mg twice daily for 2 days, then 400 mg once daily for up to 8 days and unfractionated heparin 5000 UI thrice daily until the end of hospitalization. Methylprednisolone 0.5 mg/kg/day for 5 days could be added if the need for supplemental oxygen was 6 L/min or more.	**Discharge from hospital** Hospitalisation was maintained for 42% versus 72% of patients at day 7; and 9% versus 39% at day 10 in the colchicine and placebo groups, respectively (p=0.002) **Duration of hospitalisation** Duration: 23 (Colchicine) vs 26 (Placebo) days Time of hospitalisation, median (IQR) : Intervention: 7 (5-9) Control: 9 (7-12) p-value: 0.03 **Time to supplemental oxygen, median (IQR), days** Intervention: 4 (2-6) Control: 6.5 (4-9) p-value: <0.001 **Need for supplemental oxygen** Day 2, 53% vs 83% (Colchicine vs Placebo) Day 6, 24% vs 56% (Colchicine vs Placebo) Log-rank, p=0,01 **Adverse events** The majority of adverse events were mild, did not differ significantly between groups and did not lead to patient withdrawal. Diarrhoea was more frequent in the Colchicine group (p = 0.26). Cardiac adverse events were absent. **Progression to ICU** Control: 4/37 vs Intervention: 2/38 **Length of ICU stay** 11 (Control, n=4) vs 12 (Intervention, n=2) days No variation

Citation	Study design	Population (n)	Treatment	Main findings
Salehzadeh, F *et al.* Research Square 2020[12] Pre-print	RCT, single centre 21 May to 20 June 2020.	Setting: Iran n= 50 (Hydroxycholorquine and Colchicine) n= 50 (Hydroxycholorquine and placebo) 100 patients **hospitalised** with COVID-19; median age 56, control 55.56 vs intervention 56.56 years Female 69%, control 56% vs intervention 62% Comorbidities (% intervention; % control): diabetes mellitus (10; 12), ischemic heart disease (12; 18), hypertension (6; 16), cancer/neoplastic disorder (2; 2), COPD (0; 8), renal failure (8; 2), hypothyroidism (2; 2) Inclusion criteria: Pulmonary involvement seen in CT-Scan compatible with COVID-19 and Positive PCR of COVID-19 Exclusion: Sensitivity to any medications of regimens, renal failure, heart failure, pregnancy, participating in another clinical study and refusal to participate in the study before or during the follow-up period	Treatment Colchicine (1 mg) Co-Intervention: Standard care Duration : 6 days Control Placebo tablet with no therapeutic effects in addition to standard care (hydroxychloroquine) Duration : 6 days	**Length of hospitalisation (mean)** 6.28 days (Colchicine) vs 8.12 days (Placebo), p<0.001

Table 2. Characteristics of excluded studies

Citation	Type of record	Reason for exclusion
Brunetti L, Diawara O, Tsai A, *et al.* Colchicine to weather the cytokine storm in hospitalized patients with COVID-19. *Journal of Clinical Medicine* 2020;9(9):2961.	Journal article	Wrong study design (cohort)
Cantini F, Goletti D, Petrone L, *et al.* Immune therapy, or antiviral therapy, or both for COVID-19: a systematic review. *Drugs* 2020;80(18):1929-46.	Journal article	Systematic review synthesising previously included RCT(s)[8] and other ineligible study designs
Corral P, Corral G, Diaz R. Colchicine and COVID-19. *The Journal of Clinical Pharmacology* 2020;60(8):978.	Journal article (letter)	Wrong study design
McEwan T & Robinson PC. A systematic review of the infectious complications of colchicine and the use of colchicine to treat infections. *Seminars in Arthritis and Rheumatism* 2020;51(1):101-12.	Journal article	Systematic review synthesising previously included RCT(s)[8] and other ineligible study designs
Papadopoulos C, Teperikidis E, Mouselimis D, *et al.* Colchicine as a potential therapeutic agent against cardiovascular complications of COVID-19: an exploratory review. *SN Comprehensive Clinical Medicine* 2020;2(9):1-11.	Journal article	Wrong study design (hypothesis-generating review)
Kobak S. COVID-19 infection in a patient with FMF: does colchicine have a protective effect? *Annals of the Rheumatic Diseases* 2020; 0(0):1-2.	Correspondence in journal	Wrong outcomes
Scarsi M, Piantoni S, Colombo E, *et al.* Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome. *Annals of the Rheumatic Diseases* 2020;79:1286-9.	Journal article	Wrong study design (cohort)
Vrachatis DA, Giannopoulos GV, Giotaki SG, *et al.* Impact of colchicine on mortality in patients with COVID-19. A meta-analysis. *Hellenic Journal of Cardiology* 2021 Jan 6;S1109-9666(20)30285-2.	Journal article	Systematic review synthesising previously included RCT(s)[8,9] and other ineligible study designs

Table 3. Characteristics of planned and ongoing studies

Citation	Study design	Population (n)	Treatment
Azienda Ospedaliero - Universitaria di Parma. EUCTR2020-001258-23-IT, first registered 20 April 2020	Randomised controlled trial with parallel assignment	An estimated 310 patients will be recruited	Patients will be randomised to standard of care or **colchicine in tablet form**
Dalili N, Kashefizadeh A, Nafar M, et al. *Adding colchicine to the antiretroviral medication - lopinavir/ritonavir (Kaletra) in hospitalized patients with non-severe Covid-19 pneumonia: a structured summary of a study protocol for a randomized controlled trial.* Trials 2020;21:489 AND Shahid Beheshti University of Medical Sciences. NCT04360980, first registered 24 April 2020	Randomised controlled trial with parallel assignment	An estimated 80 participants will be recruited	Participants will be randomised to standard treatment (3 g vitamin C, 400 mg tiamine, selenium, 500 mg omega-3, vitamins A and D, azithromycin, ceftriaxone and Kaletra 400 twice a day for 10 days) or **standard treatment plus 1.5 mg colchicine (loading dose) followed by 0.5 mg colchicine orally twice daily**
Dhaka Medical College. NCT04527562, first registered 26 August 2020	Randomised controlled trial with parallel assignment	An estimated 300 participants will be recruited	Participants will be randomised to standard treatment per the national guidelines of Bangladesh plus placebo or **colchicine at a starting dose of 1.2 mg (single or 12 hourly divided dose), and 0.6 mg daily thereafter for 13 days. In the case of gastrointestinal compliants, omeprazole and antiemetic will be prescribed**
Estudios Clínicos Latino América. NCT04328480, first registered 31 March 2020	Randomised controlled trial with parallel assignment	An estimated 2500 participants will be recruited	Participants will be randomised to local standard of care or **local standard of care plus colchicine, preferentially administered orally (otherwise via nasogastric**

Citation	Study design	Population (n)	Treatment
			route, in the case of ventilation or contraindications to oral route) at dosage schedules dependent on concomitant lopinavir/ritonavir treatment
FFIS. EUCTR2020-001511-25-ES, first registered 15 April 2020	Randomised controlled trial with parallel assignment	An estimated 102 patients will be recruited	Patients will be randomised to unspecified control or **0.5 mg colchicine**
Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia. NCT04350320, first registered 17 April 2020	Randomised controlled trial with parallel assignment	An estimated 102 participants will be recruited	Participants will be randomised to standard therapy or **standard therapy plus colchicine at a loading dose of 1.5 mg (1 mg and 0.5 mg two hours later), with 0.5 mg every 12 hours thereafter for seven days and 0.5 mg every 24 hours until the completion of 28 days. Dosage will be adjusted in participants receiving lopinavir/ritonavir**
Fundación Universitaria de Ciencias de la Salud. NCT04539873, first registered 7 September 2020	Randomised controlled trial with parallel assignment	An estimated 128 participants will be recruited	Participants will be randomised to standard treatment per the Colombian guidelines or **colchicine 1.5 mg on the first day, followed by 0.5 mg every 12 hours on days 2 to 7 and 0.5 mg per day until completion on day 14 ± 1 days**
Indira Gandhi Medical College & Hospital-Shimla, Department of Medicine. CTRI/2020/09/028088, first registered 28 September 2020	Randomised controlled trial with parallel assignment	An estimated 34 participants will be recruited	Participants will be randomised to receive standard of care or **standard of care plus colchicine 0.6 mg orally every 12 hours, aspirin 325 mg orally every 6 hours and montelukast 10 mg orally once a day until discharge**
Insel Gruppe AG - Bern University Hospital, Department of Cardiology. EudraCT 2020-002234-32, first registered 26 October 2020	Randomised controlled trial with parallel assignment	An estimated 420 subjects will be recruited	Participants will be randomised to receive edoxaban tablets administered orally or **colchicine tablets administered orally**
Instituto de Investigación Marqués de Valdecilla. NCT04416334, first registered 4 June 2020	Randomised controlled trial with parallel assignment	An estimated 954 participants will be recruited	Participants will be randomised to receive symptomatic treatment (paracetamol and treatment based on physician recommendation) or **symptomatic treatment plus colchicine 0.5 mg orally twice daily for three days, then once daily for 18 days**
Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran. NCT04367168, first registered 29 April 2020	Randomised controlled trial with parallel assignment	An estimated 174 participants will be recruited	Participants will be randomised to placebo tablets taken orally, 1.5 tablets on day 1 and half a tablet twice daily for 10 days thereafter, or **colchicine 1 mg at the same dosing frequency**
Kermanshah University of Medical Sciences. NCT04392141, first registered 18 May 2020	Randomised controlled trial with parallel assignment	An estimated 200 participants will be recruited	Participants will be randomised to standard treatment based on national recommendations or **standard treatment plus colchicine and a herbal extraction containing phenolic monoterpene fractions**
Liaquat University of Medical & Health Sciences. NCT04603690, first registered 27 October 2020	Randomised controlled trial with parallel assignment	An estimated number of participants for recruitment is not provided	Participants will be randomised to receive standard care as per hospital guidelines or **colchicine at an initial dose of 1.5 mg (1 mg initially and 0.5 mg two hours later), followed by 0.5 mg every 12 hours for seven days or 0.5 mg every 24 hours for 14 days (dose halved in patients receiving ritonavir or lopinavir, and those with impaired renal clearance)**
Lomonosov Moscow State University Medical Research and Educational Center. NCT04403243, first registered 27 May 2020	Randomised controlled trial with parallel assignment	An estimated 70 participants will be recruited	Participants will be randomised to ruxolitinib 5 mg taken orally twice daily for 10 days, or **colchicine 0.5 mg taken orally twice daily during the first three days and then 0.5 mg taken orally once daily if weight is < 86 kg, or twice daily if weight is > 86 kg, for seven days**
Maimonides Medical Center. NCT04363437, first registered 27 April 2020	Randomised controlled trial with parallel assignment	An estimated 70 participants will be recruited	Participants will be randomised to usual care or **1.2 mg colchicine (loading dose) followed by 0.6 mg two hours later, in the absence of severe gastrointestinal**

Citation	Study design	Population (n)	Treatment
			symptoms, on the first day; followed by 0.6 mg twice daily for 14 days or until discharge
Maria Joyera Rodríguez. NCT04492358, first registered 30 July 2020	Randomised controlled trial with parallel assignment	An estimated 144 participants will be recruited	Participants will be randomised to standard of care or **colchicine 0.3 mg/kg/day (with adjustments for age, weight and kidney function) plus prednisone 60 mg/day for three days, followed by 0.5 mg/day colchicine for a further 14 days**
Mashhad University of Medical Sciences. IRCT20200408046990N2, first registered 25 April 2020	Randomised controlled trial with parallel assignment	An estimated 40 patients will be recruited	Patients will be randomised to placebo tablets once daily for two weeks or **1 mg colchicine tablets once daily for two weeks**
Medical Biology Research Center, Kermanshah University Medical Sciences. IRCT20150623022884N3, first registered 18 November 2020	Randomised controlled trial with parallel assignment	An estimated 120 participants have been recruited	Participants are randomised to receive standard care (Kaletra or hydroxychloroquine, naproxen or other accessory drugs) or **standard care plus MAB98 (colchicine, thymoquinone and thymol fractions from Colchicum autumnale, Nigella sativa and Trachyspermum ammi) capsules 125/250 mg two or three times daily, for 6 days (outpatients) or 12 days (inpatients)**
Miami Cardiac and Vascular Institute. NCT04510038, first registered 12 August 2020	Randomised controlled trial with parallel assignment	An estimated 75 participants with cardiac injury will be recruited	Participants will be randomised to standard of care or **standard of care plus colchicine 0.6 mg twice daily for 30 days, with decreased dose of 0.3 to 0.6 mg daily in the case of gastrointestinal intolerance, CYP3A4 or protease inhibitor, chronic kidney disease at stage 4 or above, end stage renal disease, or dialysis**
Saghafi, F. IRCT20190810044500N5, first registered 18 May 2020	Randomised controlled trial with parallel assignment	An estimated 200 patients will be recruited	Patients will be randomised, in addition to standard treatment of 200 mg hydroxychloroquine daily, to two tablets of placebo for the first to the third day and one daily dose for 12 days thereafter; or **0.5 mg colchicine for the first to the third day and 1 mg daily for 12 days thereafter in addition to 200 mg hydroxychloroquine daily**
Sociedad Española de Cardiología. EUCTR2020-001841-38-ES, first registered 26 May 2020	Clinical trial with single group assignment	An estimated 240 patients will be recruited	Patients will receive 0.5 to 1 mg colchicine
University of California. NCT04355143, first registered 21 April 2020	Randomised controlled trial with parallel assignment	An estimated 150 participants will be recruited	Patients will be randomised to current care as determined by treating physician or **current care plus 0.6 mg colchicine tablets taken orally every 12 hours for 30 days**
University of Perugia. NCT04375202, first registered 5 May 2020	Randomised controlled trial with parallel assignment	An estimated 308 participants will be recruited	Participants will be randomised to current care or **current care plus 1 mg colchicine twice daily (0.5 taken orally every 8 hours) for 30 days, with dosage halved for those weighing < 100 kg**
University of Sao Paulo. NCT04724629, first registered 26 January 2021	Randomised controlled trial with parallel assignment	An estimated 60 participants will be recruited	Participants will be randomised to receive standard of care (corticosteroids and antivirals), IL-17 inhibitor (ixekizumab) 80 mg/week for four weeks, low-dose IL-2 (aldesleukin) 1.5 million IU/day for seven days or **indirect IL-6 inhibitor (colchicine) 0.5 mg every 8 hours for three days followed by 0.5 mg twice daily for four weeks**
Yale University. NCT04472611, first registered 15 July 2020	Randomised controlled trial with parallel assignment	An estimated 824 participants will be recruited	Participants will be randomised to standard of care or **standard of care plus rosuvastatin 40 mg daily and colchicine 0.6 mg twice daily for three days, and 0.6 mg once daily thereafter for the duration of hospitalisation**

Table 4.1: Summary of findings for non-hospitalised patients with COVID-19 (Tardif *et al.* (2021)[3])

Author(s): M.McCaul, A. Brand
Question: Colchicine compared to Standard treatment or placebo for non-hospitalised patients with COVID-19
Setting: Canada, USA, South Africa; and unspecified countries in Europe and South America

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	Standard treatment or placebo	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality											
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	5/2235 (0.2%)	9/2253 (0.4%)	**OR 0.56** (0.19 to 1.67)	**2 fewer per 1,000** (from 3 fewer to 3 more)	⊕◯◯◯ VERY LOW
Hospitalisation for COVID											
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	101/2235 (4.5%)	131/2253 (5.8%)	**OR 0.79** (0.60 to 1.03)	**12 fewer per 1,000** (from 22 fewer to 2 more)	⊕⊕◯◯ LOW
Mechanical ventilation											
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	11/2235 (0.5%)	21/2253 (0.9%)	**OR 0.53** (0.25 to 1.09)	**4 fewer per 1,000** (from 7 fewer to 1 more)	⊕⊕◯◯ LOW
Any SAE											
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	108/2235 (4.8%)	139/2253 (6.2%)	**OR 0.77** (0.59 to 1.09)	**14 fewer per 1,000** (from 24 fewer to 5 more)	⊕⊕◯◯ LOW
Any AE											
1	randomised trials	serious [a]	not serious	not serious	not serious	none	532/2235 (23.8%)	344/2254 (15.3%)	**OR 1.78** (1.50 to 2.00)	**90 more per 1,000** (from 60 more to 112 more)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **OR:** Odds ratio

Explanations
a. Downgraded by 1 due to serious risk of bias in randomisation and missing outcome data
b. Downgraded by 2 due to very serious imprecision
c. Downgraded by 1 due to serious imprecision

Table 4.2: Summary of findings for hospitalised and non-hospitalised patients with COVID-19 (Deftereos *et al.* (2020)[10], Lopes *et al.* (2021)[11], Tardif *et al.* (2021)[3])

Author(s): M.McCaul, A. Brand
Question: Colchicine compared to Standard care or placebo for hospitalised and non-hospitalised patients with COVID-19
Setting: Canada, USA, South Africa; and unspecified countries in Europe and South America

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	standard care	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality											
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	6/2329 (0.3%)	15/2344 (0.6%)	**OR 0.41** (0.16 to 1.03)	**4 fewer per 1,000** (from 5 fewer to 0 more)	⊕⊕◯◯ LOW
Any SAE											
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	110/2329 (4.7%)	141/2344 (6.0%)	**OR 0.78** (0.60 to 1.00)	**13 fewer per 1,000** (from 23 fewer to 0 fewer)	⊕⊕◯◯ LOW
Any AE											
2	randomised trials	serious [a]	not serious	not serious	not serious	none	542/2273 (23.8%)	352/2290 (15.4%)	**OR 1.72** (1.49 to 2.00)	**84 more per 1,000** (from 59 more to 113 more)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio

Explanations
a. Downgrade by 1 for serious risk of bias across trials; all information from studies with some concerns or at high risk of overall bias
b. Downgrade by 1 for serious imprecision

Table 5.1: Quality appraisal: overall risk of bias for the primary outcome (2-grade increase on an ordinal scale for clinical deterioration) from Bollig *et al.*(2020)[4] (Deftereos *et al.* (2020)[10])

Bias	Author's judgment	Support for judgment
Randomisation	Low	Quote: "Eligible patients were randomly assigned (1:1) to either the control group or the colchicine group. The randomization sequence was prepared by a statistician not involved in the trial using R software version 3.6.2 (R Project for Statistical Computing), and the corresponding assignment was provided to site coordinators electronically on each patient enrollment." Comment: There are minor imbalances in baseline data between the two groups (see Table 1). These imbalances do not systematically favor one group over the other, and we do not consider that they could impact the results of the trial.
Deviations from intervention	Some concerns	Comment: Unblinded study. No indication of participant crossover. Outcome data were analyzed by using intention-to-treat analysis.
Missing outcome data	Low	Comment: 110 randomized/105 analyzed. Risk assessed to be low for the outcomes: Mortality. Score 6 and above. Score 7 and above. Serious adverse events
Measurement of the outcome	Some concerns	Comment: Mortality is an observer-reported outcome not involving judgement. Score 6 and above and Score 7 and above are outcomes that reflect decisions made by the intervention provider. We consider that the assessment of Mortality and Score 7 and above cannot possibly be influenced by knowledge of the intervention assignment. Risk assessed to be low for outcomes: Mortality. Score 7 and above. For Score 6 and above, although the assessment could possibly be influence by knowledge of the intervention assignment, we did not consider this likely to have happened in the context of a pandemic. Serious adverse events may contain both clinically- and laboratory-detected outcomes, therefore it can be influenced by knowledge of the intervention assignment, but is not likely to. Risk assessed to be some concerns for outcomes: Score 6 and above. Serious adverse events.
Selection of the reported results	Low	Comment: the protocol and statistical analysis plan were available. Risk assessed to be low for the outcomes: Mortality. Score 6 and above. Score 7 and above. Serious adverse events.
Overall risk of bias	**Some concerns**	

Table 5.2: Quality appraisal: overall risk of bias for the primary outcome (time of need for supplemental oxygen; time of hospitalization; need for admission and length of stay in ICU; and death rate and causes of mortality) from covid-nma.com, adapted by review team following publication (Lopes *et al.* (2020)[11])

Bias	Author's judgment	Support for judgment
Randomisation	Low	Quote: "The randomization was performed 1:1 for placebo or colchicine by using the online tool at https://www.randomizer.org/." Comment: Allocation sequence random. Allocation sequence was concealed.
Deviations from intervention	Low	Comment: Double-blinded study. Data were analyzed using intention-to-treat analysis.
Missing outcome data	Low	Comment: 75 randomized, 72 analyzed. Following contact with authors, 2 patients who discontinued due to ICU admission were discharged after 23 and 26 days (outcome known). Safety event unknown in these 2 patients.
Measurement of the outcome	Low	Comment: This is a double-blinded study (participants and clinicians/carers). Mortality is an observer-reported outcome not involving judgement. For the outcome incidence of WHO score 7 and above, we consider that the assessment cannot possibly be influenced by knowledge of the intervention assignment. Pneumonia (assessed via imaging) was the only serious adverse event reported and therefore not influenced by judgement. Risk assessed to be low for outcomes: Mortality. Incidence of WHO score 7 and above. Serious adverse events. Note: Clinical improvement (defined as discharge from hospital) and incidence of WHO score 6 and above reflects decisions made by the intervention provider. Furthermore, adverse events reported contain both clinically- and laboratory-detected events. Assessment of these outcomes could possibly be influenced by knowledge of the intervention assignment but we did not consider this likely to have happened in the context of a pandemic. Risk assessed to be some concerns for the outcomes: Incidence of WHO score 6 and above. Adverse events.
Selection of the reported results	Some concerns	Comment: No protocol and statistical analysis plan were available. Risk assessed to be some concerns for the outcome: Mortality. Incidence of clinical improvement. Incidence of WHO score 6 and above. Incidence of WHO score 7 and above. Adverse events. Serious adverse events
Overall risk of bias	**Some concerns**	

Table 5.3: Quality appraisal: overall risk of bias for the primary outcome (length of hospitalization; symptoms and co-existed disease) from covid-nma.com (Salehzadeh *et al.* (2020)[12])

Bias	Author's judgment	Support for judgment
Randomisation	Some concerns	Quote: "Patients were randomized in 1:1 allocation in two groups (group-A and group-B) which contains 50 patients" Comment: No information on allocation sequence. No information on allocation concealment. Allocation sequence probably random.
Deviations from intervention	Some concerns	Quote: "prospective, open-label, randomized and double blind clinical trial"; "The participants of the placebo group were received a similar tablet without therapeutic effects" Comment: Blinding unclear as no description provided and contradictory descriptions used in study. No information on cross-over (no flow chart) No information on administration of co-intervention of interest: antivirals, anticoagulants. biologics, corticosteroids. Data analyzed appropriately; participants analyzed according to their intervention assignment.
Missing outcome data	Low	Comment: 100 patients randomized; 100 patients analyzed. Risk assessed to be low for the outcome: Mortality.
Measurement of the outcome	Low	Comment: Unclear blinding Mortality is observer-reported and not involving judgement. Risk assessed to be low for the outcome: Mortality.
Selection of the reported results	Some concerns	Comment: Neither the protocol nor the statistical analysis plan was available. The prospective registry was available. The mortality outcome was not listed. Risk assessed to be some concerns for the outcome: Mortality.
Overall risk of bias	**Some concerns**	

Table 5.4: Quality appraisal: overall risk of bias for the primary outcome (composite of death or hospitalisation for COVID-19) by reviewers (Tardif *et al.* (2020)[3])

Bias	Author's judgment	Support for judgment
Randomisation	Some concerns	Comment: No explicit information regarding randomisation, but both the publication and trial registry indicate that participants were randomised. No information provided on allocation concealment. No formal hypothesis tests were conducted, but there is no apparent catastrophic baseline imbalance between the two groups.
Deviations from intervention	Low	Comment: The publication describes the trial as 'double-blind', the trial registry indicates single masking of the participants. As the publication also refers to unblinding at database lock, the other blinded party was likely the statistician. It is also very unlikely that people delivering the interventions were blinded. Deviations reported are expected to arise in usual care e.g. death, withdrew consent, hospitalised and intubated etc. The authors report that an intention to treat analysis was conducted. A total of 18/4506 (0.4%) randomised participants were not included in the ITT analysis (numbers by trial arm unspecified).
Missing outcome data	High	Comment: 125/4506 (28%) participants in the total group did not have data available. 43/2235 (19%) participants in the colchicine and 64/2253 (28%) participants in the control arm did not have data available. The method used to account for missing data in the ITT is not specified. Some missing data originated from participants who died, or were hospitalised and intubated. With high attrition overall and in the control arm, as well as 9% differential attrition, some missingness could and is likely to be dependent on the true value of the outcome.
Measurement of the outcome	Low	Comment: Very little information on outcome assessment, but given the objective nature of the outcomes their assessment was likely appropriate. No evidence that a different method was used to ascertain the outcome across trial arms. The trial is reported as 'double-blind', with participants and statistician(s) likely the blinded groups. The composite endpoint is not an observer-reported outcome involving judgment.
Selection of the reported results	Low	Comment: A statistical analysis plan was approved, but is not available in the public domain. The database was locked before unblinding (likely of the statistician). Analysis intentions are not available in the public domain to enable an assessment of selective outcome reporting based on eligible outcome measurements or analyses of the data, but this is judged as unlikely.
Overall risk of bias	**High**	

Appendix 1: Search strategy

Epistemonikos (title:("covid-19" OR covid19 OR "covid 19" OR coronavirus* OR coronovirus* OR corona-virus OR corono-virus* OR nCoV*) OR abstract:("covid-19" OR covid19 OR "covid 19" OR coronavirus* OR coronovirus* OR corona-virus OR corono-virus* OR nCoV*)) AND (title:(colchicine) OR abstract:(colchicine)) **Records retrieved: 36 in initial review; 53 in first update; 82 in second update (20 relevant to PICO question)**
Cochrane COVID Study Register Searched the register for the term "colchicine" **Records retrieved: 31 in initial review; 45 in first update; 68 in second update (15 relevant to PICO question)**
www.covid-nma.com Searched the website for the term "colchicine" **Records retrieved: 3**

Appendix 2: 7-point modified ordinal scale used by Deftereos *et al.* (2020)[9]

DESCRIPTOR	LEVEL
Ambulatory, normal activities	1
Ambulatory, but unable to resume normal activities	2
Hospitalised, not requiring supplemental oxygen	3
Hospitalised, requiring supplemental oxygen	4
Hospitalised, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both	5
Hospitalised, requiring extracorporeal membrane oxygenation, invasive mechanical ventilation, or both	6
Death	7

Appendix 4: standard 10-point WHO ordinal scale[6] used in evidence profiles by Bollig *et al.* (2020)[3]

PATIENT STATE	DESCRIPTOR	LEVEL
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised moderate disease	Hospitalised; no oxygen therapy	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2≥200	7
	Mechanical ventilation pO_2/FiO_2 <150 (SpO_2/FiO_2<200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis or ECMO	9
Dead	Dead	10

Appendix 5: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** *Ambulatory and hospitalised patients:* High [ ] Moderate [ ] Low [x] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*Ambulatory patients:* One RCT of low certainty for the outcome of hospitalisation (Tardif *et al*.). Randomisation was unclearly reported (refer to GRADE table above), and the study is in pre-print format. *Hospitalised patients:* Three RCTs, one still in pre-print form. Two of three RCTs (Salehzadeh *et al.;* Deftereos *et al.*) were not powered to detect a difference in mortality; while a third reached its intended sample size (Lopes *et al.).*
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** *Ambulatory patients:* Large [ ] Moderate [ ] Small [x] None [ ] Uncertain [ ] *Hospitalised patients:* Large [ ] Moderate [ ] Small [ ] None [ ] Uncertain [x]	*Ambulatory patients:* Small reduction in hospitalisation in PCR-confirmed ambulatory cases: NNT to prevent 1 hospitalisation is 7 -- Hospitalisation for PCR-confirmed cases: 14 fewer per 1,000 (from 25 fewer to 1 fewer). No significant benefit in terms of mortality or progression to WHO stage 7 or above. *Hospitalised patients:* A meta-analysis (Figure 2, above) in hospitalised patients found no significant difference in mortality at day 14 to day 28 (OR 0.21; 95% CI 0.03 to 1.28; 2 RCTs). The effect of colchicine on progression to mechanical ventilation in hospitalised patients is uncertain.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** *Ambulatory and hospitalised patients:* High [ ] Moderate [x] Low [ ] Very low [ ] High quality: confident in the evidence Moderate quality: mostly confident, but further research may change the effect Low quality: some confidence, further research likely to change the effect Very low quality: findings indicate uncertain effect	*Ambulatory and hospitalised patients:* An increased risk of any adverse event was noted, with the listed events being those associated with the use of colchicine at the usual doses in the management of acute gout – low to moderate certainty evidence.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** *Ambulatory and hospitalised patients:* Large [ ] Moderate [x] Small [ ] None [ ]	*Ambulatory and hospitalised patients:* Similar amongst hospitalised and non-hospitalised patients. • *Serious adverse events:* No significant increase in SAEs; NNH 77; 13 fewer per 1,000 (from 23 fewer to 0 fewer). • *Adverse events:* Significant increase in AEs. NNH 12; 84 more per 1,000 (from 59 more to 113 more).
BENEFITS & HARMS	**Do desirable effects outweigh undesirable harms?** *Ambulatory patients:* Favours intervention [ ] Favours control [ ] Intervention = Control *or* **Uncertain** [x] *Hospitalised patients:* Favours intervention [ ] Favours control [x] Intervention = Control *or* **Uncertain** [ ]	*Ambulatory patients:* There is uncertainty, as there is a small benefit in terms of hospitalisation whilst gastrointestinal adverse events are relatively common. *Hospitalised patients:* The harms of colchicine outweigh the benefits in this patient cohort.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	The product is registered in South Africa and is procured in the public sector.

<table>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [x] Less intensive [ ] Uncertain [ ]</td><td>Price of medicines/ treatment course:
<table><tr><th>Medicine</th><th>Tender price (ZAR)*</th><th>SEP (ZAR)**</th></tr><tr><td>Colchicine 0.5mg, 33 tablets: 0.5 mg 12 hourly x 3days, then daily x27days (Tardif et al, non-hospitalised)</td><td>60.58</td><td>142.51</td></tr></table>* Contract circular RT289-2019 (1 Feb 2021) - 12 tabs = R22.03
**SEP database, 12 tabs = R51.82
Additional resources: Management of common gastrointestinal adverse effects.</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?

Minor [x] Major [ ] Uncertain [ ]

Is the option acceptable to key stakeholders?
Yes [x] No [ ] Uncertain [ ]</td><td>There are no available local survey data to indicate preferences in relation to colchicine use in COVID-19.

However, the Committee was of the opinion that there would be minor variability amongst stakeholders for the use of colchicine compared to hospitalisation.</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes [ ] No [x] Uncertain [ ]</td><td>Costs are minimal; colchicine is SAHPRA registered and available in private sector and is on tender in the public sector.</td></tr>
</table>

Appendix 6: Updating of rapid report

Date	Signal	Rationale
28 January 2021	Preprint of COLCORONA trial	The study results of the COLCORONA trial, evaluating the efficacy of colchicine in non-hospitalized patients with COVID-19, published in preprint format

Version	Date	Reviewer(s)	Recommendation and Rationale
First	6 August 2020	OA, AB, AH, RdW, AG	Treatment of COVID-19 in hospitalised patients with colchicine is not currently recommended. There is currently insufficient evidence of clinically-relevant benefits and an uncertain risk of adverse effects.
Second	20 October 2020	MM, AB, RdW, AG	Treatment of COVID-19 in hospitalised patients with colchicine is not currently recommended. There is currently insufficient evidence of clinically-relevant benefits and an uncertain risk of adverse effects.
Third	12 February 2021	MM, AB, RdW, AG	We suggest not to use colchicine for the treatment of COVID-19 in hospitalised and non-hospitalised patients, unless in the context of an approved clinical trial. The evidence of efficacy and safety is uncertain at this point, with insufficient evidence of clinically-relevant benefits, an increased risk of adverse effects, and an uncertain risk of serious adverse effects.