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

TITLE: Inhaled corticosteroids in ambulatory and hospitalised patients with COVID-19, not requiring oxygen therapy

Date: 6 June 2022 *(update of the initial report of 9 July 2021)*

Key findings

- We conducted a rapid review of the evidence for the use of inhaled corticosteroids in ambulatory and hospitalised patients with COVID-19, not requiring oxygen therapy.
- We identified 7 randomised controlled trials (RCTs) in adults that compared ICS to the standard of care, in ambulatory care.
- There was no significant difference in the proportion reporting resolution of symptoms by 28 days (relative risk (RR) 1.28, 95% confidence interval (CI) 0.87 to 1.88), based on 5 RCTs, with 3978 participants (*very low certainty evidence*).
- There was a statistically significant difference in the time to resolution of symptoms (mean 2.74 fewer days, 95% CI 5.47 fewer to 0.01 fewer days), based on two RCTs, with 363 participants (*very low certainty evidence*).
- There were no significant differences in progression to oxygen therapy (RR 1.27; 95% CI 0.90 to 1.80), mechanical ventilation (RR 1.79; 95% CI 0.86 to 3.71), hospitalisation or death (RR 0.95, 95% CI 0.61 to 1.49) (*low certainty evidence*).
- There were no significant differences in the proportion with negative SARS-CoV-2 PCR results at 14 days (RR 2.02; 95% CI 0.20 to 20.39), adverse events (RR 1.11; 95% CI: 0.73 to 1.68), or serious adverse events (RR 1.23; 95% CI: 0.48 to 3.13) (*very low certainty evidence*).

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 NEMLC COVID-19 sub-committee suggests that inhaled corticosteroids not be used routinely in ambulant or hospitalised patients with COVID-19, not requiring oxygen therapy, unless indicated for other reasons.
Rationale: There is low certainty evidence of a modest reduction in the time to self-reported resolution of symptoms, based on two open-label studies. Whether this benefit justifies the cost of providing every ambulant patient with COVID-19, or even those in higher risk groups, with inhaled corticosteroids, and the potential adverse events associated with use of these agents, is unclear. There are also concerns of national supply constraints and the negative impact on the availability of inhaled corticosteroids for use by patients with asthma or chronic obstructive pulmonary disease.
Level of Evidence: Low certainty evidence of limited benefits; very low certainty evidence for safety
Review indicator: Evidence of benefit (reduced hospitalisation, oxygen requirements, ventilation, intensive care or death).

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

NEML MAC on COVID-19 Therapeutics Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Jeremy Nel, Andy Parrish *(Chair)*, Helen Rees, Gary Reubenson *(Vice-Chair)*. Secretariat: Trudy Leong (NDoH), Milli Reddy (BHPSA).

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

PROSPERO registration: CRD42021286710

BACKGROUND

Inhaled corticosteroids (ICS) have been proposed as a potential treatment for COVID-19 in ambulant patients, based on the observation that the prevalence of chronic respiratory diseases was lower in patients hospitalised with SARS-CoV2 infection than in the general population. In theory, therefore, treatment with inhaled corticosteroids might have prevented deterioration in COVID-19 symptoms. In addition, an *in vitro* study had showed that ciclesonide reduced SARS-CoV2 replication in human tracheal epithelial cells (1-3).

RESEARCH QUESTION:

Should inhaled corticosteroids be used to treat patients with suspected or confirmed COVID-19 not requiring oxygen therapy, in hospital or in ambulatory settings?

METHODS

This is the second iteration of this rapid review. The initial review was conducted in July 2021, for which we systematically searched four electronic databases (PubMed, Epistemonikos, the Cochrane COVID Register and www.covid-nma.com). The search strategy is shown in Appendix 1. Screening of records and selection of studies was done independently and in duplicate by two reviewers (AH and VN) using Rayyan software, with conflicts resolved by input from a third reviewer (TK). Data extraction from the included studies was done independently. We did an updated search until 16 May 2022 in Cochrane library and COVID-NMA alone. Table 1 reports the main characteristics and outcomes of the included studies. The reviewers independently assessed the quality of the included randomised controlled trials (RCTs) using the Risk of Bias 2.0 (RoB 2) tool for some outcomes provided by COVID-NMA (4). The reviewers relied upon the risk of bias assessment provided by the COVID-NMA living systematic review for the outcomes of *hospitalisations and death, adverse events and serious adverse events* (5). However, for outcomes that were not relevant to COVID-NMA, but relevant to this report (*resolution of symptoms, time to resolution of symptoms, duration of hospitalisation, progression to requiring oxygen, progression to requiring mechanical ventilation, proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis*) the reviewers conducted the risk of bias assessment. Meta-analyses were carried out in RevMan using random-effects models (6). Results were reported as risk ratios in the case of dichotomous outcomes or mean differences in terms of continuous outcomes, with 95% confidence intervals. Where necessary and possible, medians and interquartile ranges (IQRs) were transformed into means and standard deviations. We used GRADEPro software to generate evidence profiles (7). One author extracted relevant study data in a narrative table of results, with results reviewed, checked, and reported independently by the second reviewer.

Eligibility criteria for review

Population: Patients with suspected or confirmed COVID-19, not requiring oxygen therapy, and treated in ambulatory care settings or hospital settings; no restriction to age or co-morbidity.

Intervention: Inhaled corticosteroids. No restriction on dose or frequency.

Comparators: Any (standard of care/placebo or active comparator).

Outcomes: Efficacy outcomes: resolution of symptoms; time to resolution of symptoms; progression to hospitalisation; duration of hospitalisation; progression to requiring oxygen; progression to requiring mechanical ventilation; proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis; mortality; Safety outcomes: adverse events, adverse drug reactions; serious adverse events.

Study designs: Systematic reviews of randomised controlled trials, and randomised controlled trials.

RESULTS

Results of the search

The initial search produced 239 records. After the removal of duplicates, 202 records were screened using title and abstract. Twenty-eight full text articles were assessed for eligibility, after exclusion of 174 records that did not meet the PICO criteria. Two RCTs were included in the qualitative synthesis as shown in the PRISMA diagram (Figure 1). A total of 14 ongoing clinical trials were identified. The updated search on 16 May 2022 identified five RCTs in COVID-NMA (5). Table 1 shows the main characteristics and outcomes of the seven included RCTs. Table 2 describes the excluded studies and Table 3 summarises the ongoing trials.

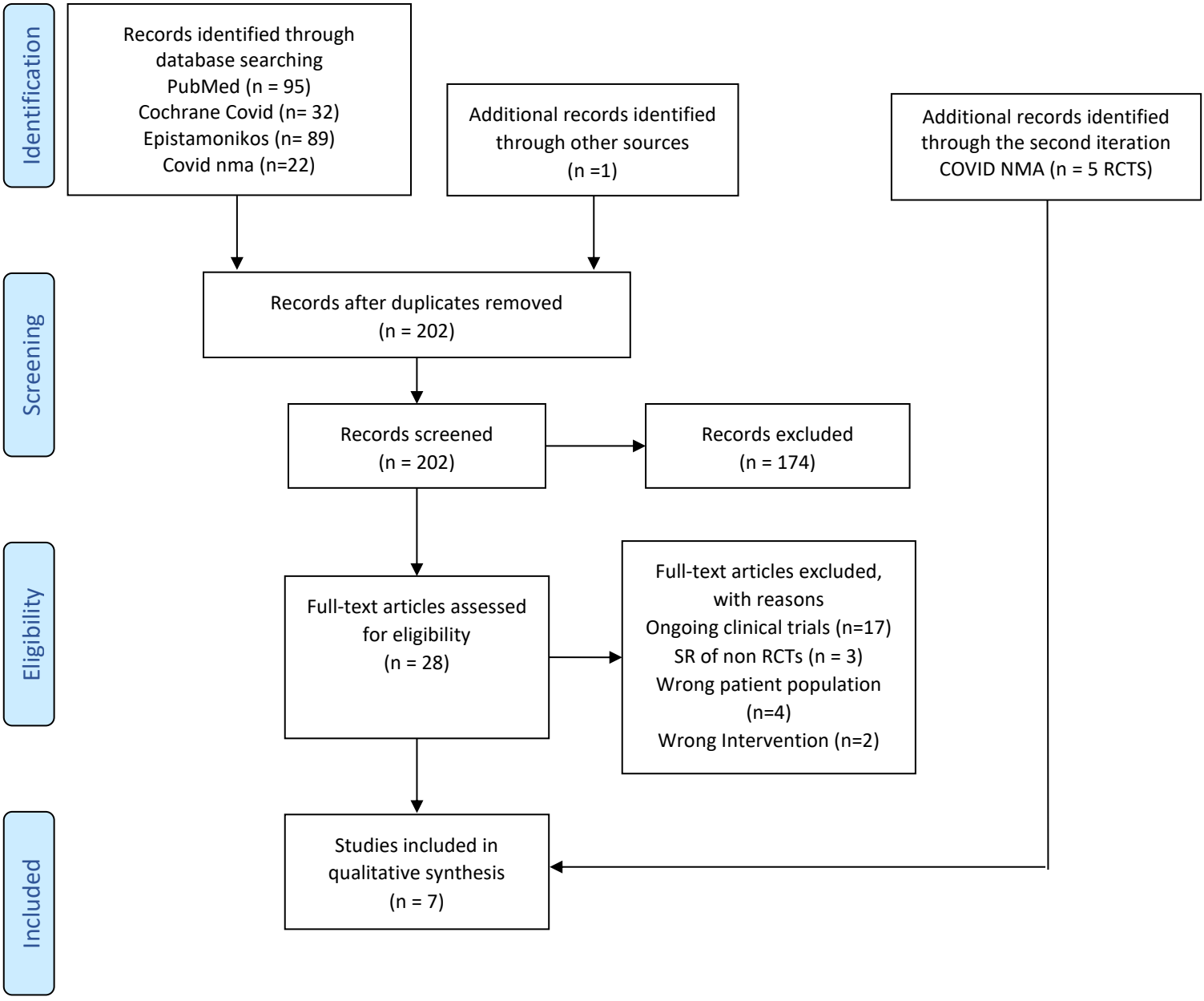

Figure 1. PRISMA flow diagram for review

Effects of the intervention

A Cochrane Review by Griesel *et al.*, based on a search conducted until 7 October 2021, was previously published (8). Griesel *et al.* included three RCTs with a total of 3607 participants, of whom 2490 had confirmed mild COVID-19 (9-11). Soon afterwards, another four RCTs were published (12-15). All results are presented for ICS compared to standard of care, in those with suspected or confirmed COVID-19. Table 4 summarises the evidence profiles for the results included. Tables 5 - 11 depict the quality appraisal of the included RCTs.

Efficacy outcomes:

Resolution of symptoms
Five RCTs reported the proportion of participants with self-reported resolution of symptoms. The evidence regarding the effect of ICS on resolution of symptoms is very uncertain (RR 1.28, 95% CI 0.87 to 1.88; I^2= 96%; 3978 participants). This represents 77 more patients reporting resolution of symptoms per 1000 patients with suspected or confirmed COVID-19 (95% CI: 36 fewer to 241 more) treated with ICS compared with standard of care.

Time to resolution of symptoms
Two RCTs reported time to self-reported resolution of symptoms. The evidence regarding the effect of ICS on time to resolution of symptoms is very uncertain (mean 2.74 fewer, 95% CI 5.47 fewer to 0.01 fewer days; I^2= 59%; 363 participants).

Progression to hospitalisation or death
Six RCTs reported progression to hospitalisation and death as a composite outcome. ICS may result in a slight reduction in progression to hospitalisation or death (RR 0.95, 95% CI 0.61 to 1.49; I^2=41%; 4019 participants; low certainty evidence). This represents 3 fewer hospitalisations or deaths per 1000 patients with suspected or confirmed COVID-19 (95% CI: 25 fewer to 31 more) treated with ICS compared with standard of care.

Duration of hospitalisation
One RCT reported on the duration of hospitalisation. The evidence regarding the effect of ICS on duration of hospitalisation is very uncertain (mean 0.4 fewer, 95% CI 4.22 fewer to 3.42 more; 61 participants)

Progression to requiring oxygen therapy
Two RCTs reported progression to requiring oxygen therapy by 28 days. ICS may result in little to no difference in progression to requiring oxygen (RR 1.27; 95% CI 0.90 to 1.80; I^2= 0%; 3223 participants; low certainty evidence). This represents 10 more requiring oxygen per 1000 patients with suspected or confirmed COVID-19 (95% CI: 4 fewer to 29 more) treated with ICS compared with standard of care.

Progression to requiring mechanical ventilation
Two RCTs reported progression to requiring mechanical ventilation by 28 days. ICS may result in little to no difference in progression to requiring mechanical ventilation (RR 1.79; 95% CI 0.86 to 3.71; I^2= 0%; 3223 participants; low certainty evidence). This represents 5 more patient requiring mechanical ventilation per 1000 patients with suspected or confirmed COVID-19 (95% CI: 1 fewer to 18 more) treated with ICS compared with standard of care.

Proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis
Two RCTs reported the proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis. The evidence regarding the effect of ICS on proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis is very uncertain (RR 2.02; 95% CI 0.20 to 20.39; I^2= 79%; 168 participants). This represents 179 more negative SARS-CoV-2 PCR on nasopharyngeal swab per 1000 patients with suspected or confirmed COVID-19 (95% CI: 140 fewer to 1000 more) treated with ICS compared with standard of care.

Mortality
This was recorded as a composite outcome with hospitalisation, as shown above.

Safety outcomes:

Adverse events

Four RCTs reported on adverse events. The evidence regarding adverse events with ICS is very uncertain (RR 1.11; 95% CI: 0.73 to 1.68; I^2= 36%; 978 participants). This represents 15 more adverse events per 1000 patients with suspected or confirmed COVID-19 (95% CI: 38 fewer to 96 more) treated with ICS compared with standard of care.

Adverse drug reactions

Neither of the RCTs reported on this outcome

Serious adverse events

Four RCTs reported on serious adverse events. The evidence regarding serious adverse events with ICS is very uncertain (RR 1.23; 95% CI: 0.48 to 3.13; I^2= 0%; 3221 participants). This represents 1 fewer serious adverse events per 1000 patients with suspected or confirmed COVID-19 (95% CI: 2 fewer to 9 more) treated with ICS compared with standard of care.

CONCLUSION

This updated systematic review of seven RCTs assessed the effectiveness of ICS patients with suspected or confirmed COVID-19 not requiring oxygen therapy, in hospital or ambulatory settings, revealed evidence of low to very low certainty for all outcomes of interest.

Reviewers: *Initial review (July 2021):* Ameer Hohlfeld, Veranyuy D. Ngah, Tamara Kredo, Renee de Waal, Andy Gray.
Update (June 2022): Ameer Hohlfeld, Sumayyah Ebrahim, Tamara Kredo, Renee de Waal, Andy Gray.

Declaration of interests: AM, TK & SE (Cochrane South Africa, South African Medical Research Council, SA GRADE Network), VN (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.

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Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Main findings
Yu LM, Bafadhel M, Dorward J, *et al*. Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial. Medrxiv. 2021 Jan 1. (9) ISRCTN86534580; EudraCT 2020-001209-22 PRINCIPLE	Multi-centre, primary care, open-label, multi-arm, prospective adaptive platform randomised trial Dates: 2020-11-27 to 2021-03-31	Setting: UK (outpatients) Previous treatments: no Number of participants: • Recruited: 4720 • Allocated: 1073 in the intervention group and 1988 in the control group • Evaluated: 787 in the intervention group and 838 in the control group (concurrent randomisation SARS-CoV-2-positive population) Inclusion criteria: • Aged ≥ 65 years • ≥ 50 years with comorbidities (heart disease, hypertension, asthma or lung disease, diabetes, hepatic impairment, stroke or neurological problems, weakened immune system, self-reported obesity) • Had ongoing symptoms from polymerase chain reaction (PCR) confirmed or suspected COVID-19 which started within the past 14 days Exclusion criteria: • Already taking inhaled or systemic corticosteroids • Unable to use an inhaler • Contraindication to inhaled budesonide Age: mean *Primary analysis population:* • 64.7 (SD 7.3) years in the intervention group • 63.8 (SD 7.8) years in the control group Concurrent randomisation population: • 64.7 (SD 7.3) years in the intervention group • 64.5 (SD 7.7) years in the control group Sex: *Primary analysis population:* • 404 (48%) male and 429 (52%) female in the intervention group • 540 (48%) male and 586 (52%) female in the control group	**Treatment** Inhaled budesonide 800µg twice daily for 14 days Co-Intervention: Usual care **Control** Usual care alone Duration of follow-up: 28 days	**Primary outcomes:** time to self-reported recovery, defined as the first instance that a participant reported feeling recovered from possible COVID-19; hospitalisation or death or both (both within 28 days) In the primary analysis population, 72 (9%) of 787 participants were admitted to hospital or died due to COVID-19 in the inhaled budesonide group (71 hospital admissions, of whom five died, and one death without hospital admission) compared with 116 (11%) of 1069 in the usual care group (114 hospital admissions, of whom nine died, and two deaths without hospital admission) **Secondary outcomes:** rating of how well participants felt (scale 1–10); time to sustained recovery (date participant first reported feeling recovered and subsequently remained well until 28 days); early sustained recovery (reported feeling recovered within the first 14 days from randomisation and remained recovered until day 28); time to initial alleviation of symptoms (date participant first reported all symptoms as minor or none); time to sustained alleviation of symptoms; time to initial reduction of severity of symptoms; contacts with health services; hospital assessment without admission; oxygen administration; intensive care unit admission; mechanical ventilation; WHO-5 Well-Being Index Analysis of secondary outcomes (table 3), using the concurrent randomisation and eligible SARS-CoV-2-positive population (787 in the budesonide group and 799 in the usual care group), showed evidence of a benefit with budesonide in early sustained recovery, the daily illness severity rating over 28 days (appendix p 231), the WHO-5 Well-Being Index, health-care service use, oxygen administration, time to sustained recovery (appendix p 232), time to sustained alleviation of all symptoms (appendix p 233), and time to reduction of symptom severity (appendix p 234). There was no clear evidence of benefit for any other secondary outcomes.

Citation	Study design	Population (n)	Treatment	Main findings
		Concurrent randomisation population: • 404 (48%) male and 429 (51%) female in the intervention group • 431 (49%) male and 455 (51%) female in the control group Proportion of confirmed infections: • Positive: 80% (833/1047) in the intervention group and 57% (1126/1959) in the control group • 20% (214/1047) SARS-CoV-2 negative, unknown, or not tested) in the intervention group and 43% (833/1959) in the control group Ethnicity: *Primary analysis population:* • White: 767 (92%) in the intervention group and 1038 (92%) in the control group • Mixed: 9 (1%) in the intervention group and 5 (< 1%) in the control group • South Asian: 43 (5%) in the intervention group and 64 (6%) in the control group • Black: 6 (1%) in the intervention group and 4 (< 1%) in the control group • Other: 8 (1%) in the intervention group and 14 (1%) in the control group • Missing: 0 in the intervention group and 1 (< 1%) in the control group *Concurrent randomisation population*: • White: 767 (92%) in the intervention group and 820 (93%) in the control group • Mixed: 9 (1%) in the intervention group and 4 (< 1%) in the control group • South Asian: 43 (5%) in the intervention group and 48 (5%) in the control group • Black: 6 (1%) in the intervention group and 3 (< 1%) in the control group • Other: 8 (1%) in the intervention group and 11 (1%) in the control group • Missing: 0 in the intervention group and 0 in the control group Received SARS-CoV-2 vaccination *Primary analysis population:*		

Citation	Study design	Population (n)	Treatment	Main findings
		• 111 (13%) in the intervention group. One-dose received: 105 (13%) and two-doses received 6 (1%) • 108 (10%) in the control group. One-dose received: 100 (9%) and two-doses received 8 (1%) *Concurrent randomisation population:* • 111 (13%) in the intervention group. One-dose received: 105 (13%) and two-doses received 6 (1%) • 108 (12%) in the control group. One-dose received: 100 (11%) and two-doses received 8 (1%) Severity of condition according to study definition: ongoing symptoms of confirmed or suspected COVID-19 (high temperature or new, continuous cough or change in sense of smell/taste, or a combination of these) within 14 days Comorbidities: asthma, chronic obstructive pulmonary disease, lung disease, diabetes mellitus, heart problems, liver disease, stroke or neurological problem, hypertension requiring medication		
Ramakrishnan, Sanjay et al. "Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial." The Lancet Respiratory Medicine, S2213-2600(21)00160-0. 9 Apr. 2021. (10) Trial registration number: NCT04416399 - STOIC	Randomised, open-label, parallel-group, phase 2 clinical trial done in the community Dates: 2020-07-16 to 2020-12-09	Setting: Oxfordshire, UK Previous treatments: no Number of participants (recruited/ allocated/evaluated): 146 recruited; of them, 73 allocated to the intervention group and 73 to the control group allocated. 70 participants in the intervention group and 69 in the control group were evaluated Inclusion criteria: • Willing and able to give informed consent for participation in the trial • Male or female • Aged ≥ 18 years • New onset of symptoms suggestive of COVID-19, e.g. new-onset cough, fever, loss of smell or taste	**Treatment** Budesonide dry powder inhaler at a dose of 400 µg per actuation (two puffs to be taken twice per day; total dose 1600 µg). **Control** Usual care Duration of follow-up: 28 days	**Primary outcome:** COVID-19-related urgent care visits, including emergency department assessment or hospitalization. • The primary outcome occurred in ten (14%) of 70 participants in the usual care group and one (1%) of 69 participants in the budesonide group (difference in proportions 0·131, 95% CI 0·043 to 0·218; p=0·004) • For the ITT population, the primary outcome occurred in 11 (15%) participants in the usual care group and two (3%) participants in the budesonide group (difference in proportions 0·123, 95% CI 0·033 to 0·213; p=0·009). **Secondary outcome:** Clinical recovery, as defined by self-reported time to symptom resolution; viral symptoms measured by the Common Cold Questionnaire (CCQ)12 and the InFLUenza PatientReported Outcome (FLUPro)13 questionnaire; blood oxygen saturations and body temperature; and SARSCoV-2 viral load

Citation	Study design	Population (n)	Treatment	Main findings
		within 7 or fewer days of participant being seen at visit 1 Exclusion criteria: • Known allergy to investigational medicine product (budesonide) • Any known contraindication to any of the investigational medicine products (budesonide) • Currently prescribed inhaled or systemic corticosteroids • Recent use, within the previous 7 days of inhaled or systemic corticosteroids • Needs hospitalisation at time of study consent • Any other significant disease or disorder which, in the opinion of the investigator, may either have put the participants at risk because of participation in the trial, or may have influenced the result of the trial, or the participant's ability to participate in the trial • Participants who had participated in another research trial involving an investigational product in the past 12 weeks Age: mean: • 44 (range 19–71) years in the intervention group • 46 (range 19–79) years in the control group Sex: • 31 (44%) male and 39 (56%) female in the intervention group • 28 (41%) male and 41 (59%) female in the control group Proportion of confirmed infections: positive: 94% (66/70) in the intervention group and 94% (65/69) in the control group Ethnicity: • White: 65 (93%) in the intervention group and 64 (93%) in the control group		• Clinical recovery was 1 day shorter in the budesonide group compared with the usual care group (median 7 days [95% CI 6 to 9] in the budesonide group vs 8 days [7 to 11] in the usual care group • The mean proportion of days with a fever in the first 14 days was lower in the budesonide group (2%, SD 6) than the usual care group (8%, SD 18; Wilcoxon test p=0·051) and the proportion of participants with at least 1 day of fever was lower in the budesonide group when compared with the usual care group. • Symptom resolution at day 14, as defined by the • FLUPro user manual, occurred in 55 (82%) participants in the budesonide group and 49 (72%) participants in the usual care group (difference in proportions 0·100, 95% CI –0·040 to 0·241; p=0·166); whereas the median time to symptom resolution as measured by the FLUPro was 3 days (95% CI 2 to 5) in the budesonide group and 4 days (3 to 6) in the usual care group (log-rank test p=0·080; appendix p 12). The mean change in FLUPro total score between days 0 and 14 in the budesonide group was –0·65 (–0·80 to –0·50) and in the usual care group was –0·54 (–0·69 to –0·40; mean difference of –0·10, 95% CI –0·21 to –0·00; p=0·044). The mean daily FLUPro scores for the total symptom burden and individual domains. • The mean change in CCQ total score between days 0 and 14 in the budesonide group was –0·49 (95% CI –0·63 to –0·350 and in the usual care group was –0·37 (–0·51 to –0·24; mean difference –0·12, 95% CI –0·21 to –0·02; p=0·016). • The proportion of days with oxygen saturations of • 94% or less, during the first 14 days, was 19% (SD 24) in the budesonide group and 22% (27) in the usual care group (Wilcoxon test p=0·627; Hodge-Lehmann median 0, 95% CI –0·07 to 0). • The median cycle threshold nasopharyngeal SARSCoV-2 viral load at day 0 was 32·1 (IQR 21·7–40·0), day 7 was 35·3 (32·4 to 40·0), and day 14 was 36·4 (34·2 to 40·0). Cycle threshold reduction was significantly different between visits 1 and 2 for both study groups (Wilcoxon matched pairs p=0·063 budesonide, p=0·004 usual care; appendix p 14); but not between groups (mean change between visits

Citation	Study design	Population (n)	Treatment	Main findings
		• Non-white: 5 (7%) in the intervention group and 5 (7%) in the control group Severity of condition according to study definition: with symptoms of COVID-19 (new-onset cough and fever or anosmia or both) within 7 days Comorbidities: cardiovascular disease, diabetes, past or current asthma		1 and 2 in the budesonide was 3·20 [95% CI 0·46 to 5·94] and usual care was 3·75 [1·00 to 6·50]; mean difference –0·55, 95% CI –2·39 to 1·29; p=0·554).
Clemency BM, Varughese R, Gonzalez-Rojas Y, Morse CG, Phipatanakul W, Koster DJ, Blaiss MS. Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA internal medicine. 2022 Jan 1; 182(1):42-9. (11) Trial registration number: NCT04377711	Multicentre, double-blind, phase 3, randomised clinical trial Number of centres: 10 Dates: 2020-06-11 to 2020-11-03	Setting: outpatient, USA Previous treatments: not reported Number of participants: Recruited: 400. Allocated: 197 in the intervention group and 203 in the control group Evaluated: 197 in the intervention group and 203 in the control group Eligibility/Inclusion criteria: • Aged >12 years • Positive SARS-CoV-2 molecular or antigen diagnostic sample obtained in the previous 72 hours • Not hospitalised or under consideration for hospitalisation • Oxygen saturation ≥93% on room air. • Able to demonstrate successful use of a metered-dose inhaler (MDI). • ≥1 of the following symptoms of COVID-19: fever, cough, or dyspnoea Exclusion criteria: • History of hypersensitivity to ciclesonide • Taken an inhaled or intranasal corticosteroid within 14 days • Taken oral corticosteroids within 90 days	**Treatment** Ciclesonide 160 µg per actuation, 2 actuations twice a day (total daily dose 640 µg) + standard care **Control** Placebo + standard care Concomitant therapy: Paracetamol, non-steroidal anti-inflammatory drugs (NSAIDS), antibiotics, antivirals, monoclonal antibodies Duration of follow-up: 30 days Treatment cross-overs: no Compliance with assigned treatment: yes	**Primary outcome:** Time to alleviation of all COVID-19-related symptoms (cough, dyspnoea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell) by day 30 In the ITT population, 139 of 197 participants (70.6%) in the ciclesonide arm and 129 of 203 participants (63.5%) in the placebo arm experienced alleviation of all symptoms. **Secondary outcomes:** Incidence of subsequent emergency department visits or hospital admissions for reasons attributable to COVID-19, incidence of hospital admissions or death, all-cause mortality, COVID-19-related mortality, percentage of participants with alleviation of COVID-19-related symptoms, time to hospital admission or death, alleviation of all COVID-19-related symptoms by days 7, 14, and 30 • Participants who received ciclesonide experienced fewer occurrences of emergency department visits or hospital admissions for reasons related to COVID-19 by day 30 compared with those who received placebo (1.0% vs 5.4%; odds ratio [OR], 0.18; 95% CI; 0.04-0.85; P = 0.03). • No other secondary outcomes reached statistical significance. The most common symptoms reported on day 30 were cough (11.7% vs 12.3%; P = 0.88), muscle pain

Citation	Study design	Population (n)	Treatment	Main findings
		• Participated in any other clinical trial or use of any investigational agent within 30 days • History of cystic fibrosis. History of idiopathic pulmonary fibrosis • Receiving treatment with hydroxychloroquine/chloroquine • Pregnant Age: mean • 43.7 (SD 17.53) years in the intervention group • 42.9 (SD 16.28) years in the control group Sex: • 85 (43%) male and 112 (57%) female in the intervention group • 94 (46%) male and 109 (54%) female in the control group Proportion of confirmed infections: Positive SARS-CoV-2 molecular or antigen diagnostic sample was inclusion criteria Ethnicity: Asian, Black or African American, Native Hawaiian or other Pacific Islander, White Severity of condition according to study definition: participants had an oxygen saturation of ≥93% on room air Comorbidities: hypertension, drug hypersensitivity, hyperlipidaemia, type 2 diabetes mellitus, asthma		(9.6% vs 8.9%; P = 0.86), and dyspnea (10.2% vs 7.9%; P = 0.49). • Participants with subsequent emergency department visit or hospital admission for reasons related to COVID-19 by day 30, %: 2 (1.0%) vs 11 (5.4%); OR 0.18; 95% CI 0.04-0.85; P = 0.03 • Participants with hospital admission or death by day 30, %: 3 (1.5%) vs 7 (3.4%); OR 0.45; 95% CI 0.11-1.84; P = 0.26 • All-cause mortality by day 30: Nil • COVID-19–related mortality by day 30: Nil • Participants with alleviation of COVID-19–related symptoms by day 7, %: 28 (14.2%) vs 29 (14.3%); OR 0.92; 95% CI 0.51-1.66; P = 0.79 • Participants with alleviation of COVID-19–related symptoms by day 14, %: 81 (41.1%) vs 76 (37.4%); OR 1.19; 95% CI 0.78-1.81, P = 0.43 • Participants with alleviation of COVID-19–related symptoms by day 30, %: 139 (70.6%) vs 129 (63.5%); OR 1.28; 95% CI 0.84-1.97; P = 0.25 Adverse events were reported by 22 participants (11.2%) in the ciclesonide arm and 29 participants (14.3%) in the placebo arm (eTable 3 in Supplement 2). Most adverse events were mild to moderate in severity.

Citation	Study design	Population (n)	Treatment	Main findings
Alsultan M, Obeid A, Alsamarrai O, Anan MT, Bakr A, Soliman N, Kurdy M, Mosa MH, Saleh Z, Hujij F, Barhoum J. Efficacy of Colchicine and Budesonide in Improvement Outcomes of Patients with Coronavirus Infection 2019 in Damascus, Syria: A Randomized Control Trial. Interdisciplinary Perspectives on Infectious Diseases. 2021 Dec 31: 2129006. (12)	Randomised controlled trial (RCT), unblinded Dates: 2021-08-01 to 2021-08-30 No trial number reported	Setting: Inpatient, single centre, Syria Previous treatments: not reported Number of participants: Recruited: 77 Allocated: 49; 14 in the budesonide intervention group, 14 in the colchicine intervention group and 21 in the control group Evaluated: 14 in the budesonide intervention group, 14 in the colchicine intervention group and 21 in the control group Inclusion criteria: • Adults (aged ≥18 years) • Patients with positive PCR test of COVID-19 virus in specimens taken from the respiratory tract • Patients with a negative PCR test but had clinical signs and symptoms of viral illness accompanied by a chest CT scan showing radiologic findings of viral pneumonia, which was defined as new, unexplained, and bilateral infiltrates on the lungs. Exclusion criteria: • Admitted for other conditions with an oxygen saturation ≥94% without viral symptoms but had infiltrations on the chest CT scan (mild form of COVID-19), received other antiviral or investigational therapies for COVID-19 • Died or admitted to ICU during the first 24 hours • Patients who committed with persistent treatment of steroid inhalers Age: mean • Not reported Sex: • 5 (36%) male and 9 (64%) female in the Budesonide intervention group • 5 (36%) male and 9 (64%) female in the Colchicine intervention group • 9 (43%) male and 12 (57%) female in the control intervention group	**Treatment** Budesonide group: 200 µg inhaled twice daily for 5 days Colchicine group: Initial dose: 1.5 mg orally followed by 0.5 mg 1 hour later on day 1, Maintenance dose: 0.5 mg orally twice daily for 4 days **Control** Standard care Concomitant therapy: oxygen supplementation, vitamins, anticoagulants, dexamethasone, prone position, noninvasive ventilation (Continuous positive airway pressure [CPAP] or Bilevel positive airway pressure [BiPAP]), antibiotics, and fluids. Duration of follow-up: NR Treatment cross-overs: no Compliance with assigned treatment: yes	No outcome was identified as primary in the article. It is not clear whether the study achieved a target sample size. • Median hospitalization days for groups with colchicine or budesonide was shorter than the group with supportive care only (8 vs 10 days, respectively). • 27 patients were followed up until weaning from oxygen, and the median days on oxygen supplementation (from the day of admission to the day they stopped using oxygen) was 20 days in the supportive group, 19 days in the colchicine group, and 20 days in the budesonide group. • 34 patients (69.3%) were discharged, 27 patients (55.1%) were followed up until weaning from oxygen and complete recovery, and 6 patients (12.2%) had been readmitted due to other conditions. • The remaining 15 patients (30.6%) were transferred to the ICU and died later. Mortality was decreased in the colchicine group (3 patients, 21.4%) compared with supportive care (7 patients, 33.3%) and budesonide groups (5 patients, 35.7%)

Citation	Study design	Population (n)	Treatment	Main findings
		Proportion of confirmed infections: • 31 had positive COVID-19 PCR results • 18 patients had negative results but had clinical signs and symptoms of viral illness together with radiologic findings on chest CT compatible with COVID-19 infection. Ethnicity: NR, likely Arab Severity of condition according to study definition: Oxygen saturation ≤93% plus at least one of the following: Respiratory rate ≥30 breaths/min, Infiltrates >50% on CT scan, Arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen ratio (FiO2) <300 mmHg. Comorbidities: kidney disease, cardiac disease, endocrine disease, neurologic disease		
Song JY, Yoon JG, Seo YB, Lee J, Eom JS, Lee JS, Choi WS, Lee EY, Choi YA, Hyun HJ, Seong H. Ciclesonide inhaler treatment for mild-to-moderate COVID-19: a randomized, open-label, phase 2 trial. Journal of Clinical Medicine. 2021 Jan; 10(16):3545. (13) Trial registration number: NCT04330586	Phase 2, multicentre, unblinded, RCT Number of centres: 6 Dates: 2020-05-08 to 2021-03-31	Setting: Inpatient, Single centre, South Korea Previous treatments: not reported Number of participants: Recruited: 68. Allocated: 61 for analysis; 35 in the intervention group, and 26 in the control group Evaluated: 35 in the intervention group, and 26 in the control group Inclusion criteria: • Patients aged ≥19 years • Mild-to-moderate COVID-19, confirmed by quantitative reverse transcription polymerase chain reaction (qRT-PCR) within 3 days of diagnosis or within 7 days from symptom onset • Low National Early Warning Score (NEWS) ranging from 0 to 4. NEWS is a scoring system based on routine physiological parameters (respiratory rate, oxygen saturation, supplemental oxygen, body temperature, systolic blood pressure, heart rate, and level of consciousness), which can be obtained easily at the bedside. For each	**Treatment** Ciclesonide 320 µg inhaled twice daily for 14 days or ciclesonide-HCQ (320 µg inhalation twice per day for 14 days/400 mg daily for 10 days) **Control** Standard care which comprised intravenous fluid, supplementary oxygen, and antibiotics, as necessary Concomitant therapy: As above Duration of follow-up: 28 days	**Primary outcome:** The primary endpoint was the SARS-CoV-2 eradication rate based on qRT-PCR on day 14 of study enrollment. SARS-CoV-2 eradication was defined as negative conversion of two consecutive negative results of qRT-PCR • SARS-CoV-2 eradication rate at day 14 was significantly higher in the ciclesonide group than in the standard care group (32.3% vs 5.0%, p = 0.021). • In the ciclesonide inhaler group, SARS-CoV-2 was negative converted in 10 patients on the 14th day of treatment, and three of them received HCQ concurrently. **Secondary outcomes:** • Rate of SARS-CoV-2 eradication at day 7 from study enrolment [Time Frame: Hospital day 7] Viral load • Time to SARS-CoV-2 eradication (days) [Time Frame: Hospital day 1, 4, 7, 10, 14, 21] Viral load • Viral load area-under-the-curve (AUC) reduction versus control [Time Frame: Hospital day 1, 4, 7, 10, 14, 21] Viral load change

Citation	Study design	Population (n)	Treatment	Main findings
		parameter, a score of zero is considered normal, and simple addition allows a total score from 0 to 20. A score of ≥5 represents the key threshold for urgent response, and patients with a score of ≥7 would be deemed to have a high-risk clinical condition requiring emergency response. Exclusion criteria: • Oxygen saturation <95% breathing room air • Pregnancy or breastfeeding • Renal impairment (estimated creatinine clearance <30 mL/min) • Hepatic dysfunction (alanine aminotransferase or aspartate aminotransferase levels more than five times the upper limit of normal) • Immunocompromising conditions • Severe uncontrolled comorbidities • Chronic airway diseases (asthma and chronic obstructive lung disease) • Contraindications for use of ciclesonide inhaler. Age: mean • 44.9 (SD: 17.9) years in the Ciclesonide group • 49.0 (SD: 16.8) years in the control group Sex: • 11 (31%) male and 24 (69%) female in the Ciclesonide group • 9 (35%) male and 17 (65%) female in the control group Proportion of confirmed infections: NR Ethnicity: NR Severity of condition according to study definition: mild-to-moderate COVID-19, confirmed by quantitative reverse transcription polymerase chain reaction (qRT-PCR). Low National Early Warning Score (NEWS) ranging from 0 to 4	Treatment cross-overs: no Compliance with assigned treatment: yes	• Time to clinical improvement (days) [Time Frame: Up to 28 days] Resolution of all systemic and respiratory symptoms for ≥2 consecutive days • Proportion of clinical failure [Time Frame: Up to 28 days] i.e. high-flow oxygen therapy or mechanical ventilation requiring salvage therapy • Safety/tolerability of ciclesonide SARS-CoV-2 eradication rates at days 7 and 10 were also higher in the ciclesonide group than in the standard care group. No significant between-group difference was observed in symptom-based clinical improvement rates at days 7, 10, and 14. However, the clinical failure rate was significantly lower in the ciclesonide group than in the standard care group (2.9% *vs* 19.2%, p = 0.034). No fatal cases were recorded in this study. Among non-pneumonic cases at study enrollment, pneumonia developed in 11.1% (3 of 27 cases) of ciclesonide group and 23.5% (4 of 17 cases) of standard care group, respectively (p = 0.273). Among the 35 patients who received ciclesonide, three complained of nausea, odynophagia, or headache after inhalation

Citation	Study design	Population (n)	Treatment	Main findings
		Comorbidities: Diabetes, hypertension, cerebrovascular diseases		
Ezer N, Belga S, Daneman N, Chan A, Smith BM, Daniels SA, Moran K, Besson C, Smyth LY, Bartlett SJ, Benedetti A. Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients: CONTAIN phase II randomised controlled trial. BMJ. 2021 Nov 2; 375 : e068060. (14) Trial registration number: NCT04435795 - CONTAIN	Multicentre, double blind, placebo controlled trial Number of centres: 3 Dates: 2020-09-15 to 2021-06-08	Setting: Outpatient, multicentre, Canada Previous treatments: not reported Number of participants: Recruited: 522 Allocated: 215 for analysis. 108 in the intervention group, and 107 in the control group Evaluated: 105 in the intervention group, and 98 in the control group Inclusion criteria: • Adults aged 18 years and older • Had polymerase chain reaction confirmed Covid-19 at enrolment • At least one of the symptoms of fever, cough (wet or dry), or shortness of breath (including dyspnoea, chest congestion, or chest tightness as synonyms) Exclusion criteria:	**Treatment** 600 µg inhaled twice a day + 200 µg intranasally once a day for 14 days **Control** Placebo Concomitant therapy: NR Duration of follow-up: 29 days Treatment cross-overs: no	**Primary outcomes:** Resolution of self-reported fever and all respiratory symptoms at day 7 of treatment. Respiratory symptoms included cough (wet or dry) or dyspnoea (which included the description of shortness of breath, chest congestion, or chest tightness as synonyms). Proportion of participants with no symptoms of cough, fever or dyspnoea at day 7 Fever and respiratory symptoms had resolved in 37% (n=76) of participants by day 7. The proportion with resolved symptoms by day 7 did not differ significantly between the intervention group (42/105, 40%) and control group (34/98, 35%). Secondary outcomes: • Hospitalization for SARS-CoV-2 related illness • Mortality [Time Frame: day 29] • Evaluation of the primary outcome at day 14, • Improvement in overall feeling (self-reported feeling

Citation	Study design	Population (n)	Treatment	Main findings
		• Already on inhaled corticosteroid medication • Currently using systemic steroids (oral or intravenous or intramuscular such as Prednisone) or use of steroids 7 days prior to enrolment • Severely ill patients at enrolment (i.e. admitted to ICU at admission) • Unable to self-administer the inhaler • Known or suspected pregnancy and breastfeeding • Known allergy to study medication or its components (non-medicinal ingredients including lactose allergy (type I)) • Patients with untreated fungal, bacterial, or tubercular infections of the respiratory tract • Current hospitalization • Current use of oxygen at home or in the hospital • Receipt of a COVID vaccine Age: reported as median and not mean • 35 (IQR: 27-47) years in the Ciclesonide group • 35 (IQR 27-45) years in the control group Sex: • 51 (49%) male and 54 (51%) female in the Ciclesonide group • 43 (44%) male and 55 (56%) female in the control group Proportion of confirmed infections: NR Ethnicity: African Canadian, Asian, White, Hispanic or Latino, Middle Eastern, South Asian, Other No vaccinated participants were included in the trial Severity of condition according to study definition: mild-to-moderate COVID-19, polymerase chain reaction confirmed COVID -19, presenting with fever, cough, or dyspnoea. Comorbidities: active cancer, asthma, diabetes mellitus, hypertension, ischaemic heart disease	Compliance with assigned treatment: yes	• much or very much better) by days 7 and 14 • Resolution of dyspnoea (defined as the absence of shortness of breath, chest tightness, or chest congestion) in the subset who reported a dyspnoea equivalent at baseline on days 7 and 14 • Improvement in cough at days 7 and 14 (defined as a 2 point decrease or a decrease to 0 on a visual analogue scale that ranged from 0 for no symptoms to 10 for severe symptoms) in those who had cough at baseline, improvement in shortness of breath as measured by the PROMIS (patient reported outcomes measurement information system) dyspnoea score, in sleep as measured by the PROMIS sleep disturbance score 4a,9 and anxiety as measured by the PROMIS emotional distress anxiety score 7a (with meaningful improvement defined as a ≥3 point change on the T score). The proportion of participants with resolved symptoms at day 14 also did not differ significantly between the two groups, with 66% (69/105) showing resolution of symptoms by day 14 in the ciclesonide group compared with 58% (57/98) in the placebo group, with an adjusted risk difference of 7.5% (95% confidence interval −5.9% to 20.8%). Six participants in the ciclesonide group and three in the placebo group were admitted to hospital. No deaths occurred. Side effects were reported in 22% (23/105) of participants in the ciclesonide group and 15% (15/98) in the placebo group (table 3).

Citation	Study design	Population (n)	Treatment	Main findings
Duvignaud A, Lhomme E, Onaisi R, Sitta R, Gelley A, Chastang J, Piroth L, Binquet C, Dupouy J, Makinson A, Lefèvre B. Inhaled ciclesonide for outpatient treatment of COVID-19 in adults at risk of adverse outcomes: a randomised controlled trial (COVERAGE). Clinical Microbiology and Infection. 2022 Mar 15: S1198-743X(22)00108-2.2. (15) Trial registration number: NCT04356495, EudraCT 2020-001435-27 COVERAGE	Phase 3, multicentre, unblinded, RCT Number of centres: 14 Dates: 2020-12-29 to 2021-07-23	Setting: Outpatient, multicentre, France Previous treatments: COVID-19 vaccine in some participants Number of participants: Recruited: NR Allocated: 217 for analysis. 110 in the intervention group, and 107 in the control group Evaluated: 110 in the intervention group, and 107 in the control group (used ITT) Inclusion criteria: • Age ≥60 years regardless of the presence of other risk factors, or ≥50 years with at least one of the following risk factors: high blood pressure, body mass index ≥30 kg/m2, diabetes, ischemic heart disease, heart failure, history of stroke, chronic obstructive pulmonary disease, stage ≥3 chronic kidney disease, solid or haematological malignancy diagnosed <5 years ago, immunosuppressive therapy, or HIV infection with CD4 <200/mm3) • COVID-19 with first symptoms ≤7 days before • Positive SARS-CoV-2 nasopharyngeal RT-PCR or antigen test • No criteria for hospitalisation or acute oxygen therapy • Written informed consent Exclusion criteria: • Inability to understand or decide on participation • Lack of health insurance • Chronic inhaled corticosteroid therapy • Hypersensitivity to ciclesonide • History of incompletely treated pulmonary tuberculosis • Pulmonary fungal infection • Inability to use the inhalation chamber • Ongoing treatment with a potent CYP3A4 inhibitor	**Treatment** ALVESCO 160 µg, two puffs twice a day using an inhalation chamber (640 µg of ciclesonide per day)for 10 days **Control** Vitamin supplementation (Azinc vitality®, 2 pills per day) for 10 days Concomitant therapy: NR Duration of follow-up: 28 days Treatment cross-overs: no Compliance with assigned treatment: yes	**Primary outcomes:** • Occurrence of grade 3-4-5 adverse events • Combination of hospitalisation, need for COVID19-related oxygen therapy at home or death During follow-up, the 217 participants had 1653 protocol visits (control 815, ciclesonide 838), 18 had 19 additional unscheduled visits (control 11, ciclesonide 8), 4 were prescribed oxygen therapy at home with no subsequent hospitalisation (control 2/107 [1.9%], ciclesonide 2/110 [1.8%]), 24 were hospitalized (control 10/107 [9.3%], ciclesonide 14/110 [12.7%]), and 2 died (control 2/107 [1.9%], ciclesonide 0). The median time between enrolment and admission to hospital was 6 days (IQR 4-9; control 5, ciclesonide 6. The median length of hospital stay was 6.5 days (IQR 4.5-14.5; control 7.0 [5.0-14.0], ciclesonide 6.5 [3.0-15.0]). In intent-to-treat analysis of observed data, 26 participants reached the composite primary endpoint by Day 14, including 12 of 106 (11.3%, 95% CI: 6.0%-18.9%) in the control arm and 14 of 106 (13.2%; 95% CI: 7.4%- 21.2%) in the ciclesonide arm. The analysis package of the primary endpoint provided robust arguments to conclude that continuing the ciclesonide arm would be futile. **Secondary outcomes:** • Adverse events of any grade, maximal follow-up • score on the WHO Ordinal Scale for Clinical Improvement • Sustained alleviation of symptoms (body temperature ≤37.5oC and reports of all following symptoms as minor or none, with no subsequent relapse: asthenia, headache, cough, retrosternal discomfort/pain, thoracic oppression, thoracic pain, dyspnoea, nausea, vomiting, diarrhoea, abdominal pain, anorexia, myalgia, or arthralgia) • Cure (participant report return to normal activity with no subsequent relapse) • RT-PCR and blood parameter evolution at D7 Table 3 shows the description of the secondary outcomes.

Citation	Study design	Population (n)	Treatment	Main findings
		Age: reported as medianand Interquartile Range [IQR] and not mean • 62 (58; IQR 67) years in the Ciclesonide group • 63 (59; IQR 70) years in the control group Sex: • 58 (53%) male and 52 (47%) female in the Ciclesonide group • 48 (45%) male and 59 (55%) female in the control group Proportion of confirmed infections: NR Ethnicity: NR Previous COVID-19 vaccine • 14 (13.1%) in the intervention group. One-dose received: 13 and two-doses received 1 • 16 (14.5%) in the control group. One-dose received: 15 and two-doses received 1 Severity of condition according to study definition: mild COVID-19 Comorbidities: Hypertension, BMI ≥30kg/m^2, diabetes, stroke, ischemic heart disease, Solid tumour or haematological malignancy <5 years, Chronic obstructive pulmonary disease, Cardiac insufficiency, HIV infection		
[a] All secondary outcome analyses were conducted on the concurrent randomization and eligible analysis population in participants with SARS-CoV-2 positive analysis population, but restricted to those in the inhaled budesonide and usual care group only.				

Table 2. Characteristics of excluded studies

Citation	Type of record	Reason for exclusion
Lawson Health Research Institute. NCT04374474, first registered 5 May 2020 Withdrawn (Study withdrawn before any enrollment (site's research goals adjustments)	Trial registry	Wrong patient population
Stanford University. NCT04193878, first registered 10 December 2019	Trial registry	Wrong patient population
Mashhad University of Medical Sciences. IRCT20200522047542N1, first registered 4 August 2020	Trial registry	Wrong patient population
Mazandaran University of Medical Sciences. IRCT20190804044429N6, first registered 20 February 2021	Trial registry	Wrong intervention
Comisión Nacional de Evaluación de Tecnologías de, Salud. Inhaled budesonide for treating COVID-19 patients	Journal article	Systematic review no RCTs included (Spanish guideline developed by Argentinian Ministry of Health. They include the two trials we've analysed in this Rapid Review)

Citation	Type of record	Reason for exclusion
Fondation Ophtalmologique Adolphe de Rothschild. NCT04361474 first registered 24 April 2020	Trial registry	Wrong intervention
Halpin DM, Singh D, Hadfield RM. Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective. European Respiratory Journal. 2020 May 1;55(5).	Journal article	Systematic review no RCTs included
Kow CS, Hasan SS. Preadmission use of inhaled corticosteroids and risk of fatal or severe COVID-19: a meta-analysis. Journal of Asthma. 2021 Jan 21:1-4.	Journal article	Systematic review no RCTs included
Ola Blennow. NCT04381364 , first registered 8 May 2020	Trial registry	Wrong patient population

Table 3. Characteristics of planned and ongoing studies

Citation	Study design	n	Treatment
Sara Verea. NCT04355637, first registered 21 April 2020	RCT with parallel assignment	300	Patients will be randomised to standard of care to treat their pneumonia or standard of care to treat their pneumonia + inhaled budesonide
Sugiyama Haruhito. JPRN-jRCTs031190269, first registered 27 March 2020	RCT with parallel assignment	90	Patients will be randomised to standard of care or Ciclesonide is inhaled three times a day at a dose of 400 microgram once a day for seven consecutive days.
University of Oxford, Clinical Trials and Research Governance. NCT04416399, registered 4 June 2020 (Terminated (Independent statistical review advice)	RCT with parallel assignment	146	Patients will be randomised to standard of care or inhaled budesonide
Respiratory Reseach Unit 237, Hvidovre Hospital. Assistance Publique - Hâ—Žpitaux de Paris l. EUCTR2020-002208-37-DK, first registered 8 June 2020	RCT with parallel assignment	138	Patients will be randomised to placebo or inhaled ciclesonide 320 mcg bid
Assistance Publique - Hâ—Žpitaux de Paris. NCT04331054, first registered 2 April 2020	RCT with parallel assignment	436	Patients will be randomised to usual practice arm will be follow during 30 days or Usual practice + inhalation SYMBICORT RAPIHALER 200/6 µg (2 puffs bid during 30 days)
Fundaciâ—Ž Eurecat. EUCTR2020-005280-31-ES, first registered 1 February 2021	RCT	200	Patients will be randomised to standard of care or inhaled budesonide / formoterol combination (BiResp Spiromax®)
Lady Hardinge Medical College - New Delhi // India. CTRI/2020/04/024948, first registered 30 April 2020	RCT with parallel assignment	120	Patients will be randomised to standard of care or oral Ivermectin 12 mg OD for 7 days or oral Hydroxychloroquine 400 mg bid Day1 followed by 200 mg bid on Days 2 to 7 or inhaled ciclesonide 200 mcg bid for 7 days
Japan Agency for Medical Research and Development (AMED). JPRN-jRCTs031200196, first registered	RCT with parallel assignment	118	Patients will be randomised to Standard care or favipiravir, oral camostat, and ciclesonide inhalation will be given for 10 days.
FundaciA³ Clinic per a la Recerca BiomA¨dica. EUCTR2020-001616-18-ES, first registered 20 April 2020	RCT with parallel assignment	300	Patients will be randomised to standard of care or Inhaled budesonide 800 microgramos
Fasa University of Medical Sciences. IRCT20200324046852N1, first registered 5 April 2020	RCT with parallel assignment	30	Patients will be randomised to standard of care or Levamisole tablet 50 mg TDS and Budesonide+ Formoterol inhaler 1 puff every 12 hours as intervention drugs in addition to standard treatment.
Fasa University of Medical Sciences. NCT04331470, first registered 2 April 2020	RCT with parallel assignment	30	Patients will be randomised to standard of care i.e. Hydroxy Chloroquine 200mg single dise Lopinavir/Ritonavir 2 tablets every 12 hours or Levamisole 50 mg tablet has to be taken 1-2 tablets every 8 hours Budesonide+Formoterol has to be inhaled 1-2 puff every 12 hours and Hydroxy Chloroquine 200mg single dise Lopinavir/Ritonavir 2 tablets every 12 hours
Tushar Patel. CTRI/2020/10/028581, first registered 20 October 2020	RCT with parallel assignment	1000	Patients will be randomised to standard of care or Budesonide Rotacaps 200 mcg BD for 10 - 14 days depending on onset of symptoms given in addition to the local standard of care
Babol University of Medical Sciences. IRCT20201024049134N1, first registered 02 November 2020	RCT with parallel assignment	80	Patients will be randomised to standard of care including famotidine, cetirizine, N-acetylcysteine, bromhexine, naproxen, and fluticasone propionate inhaler, or the intervention group will also receive the standard regimen plus two capsules of arbidol (manufactured by Pharmstandard, Russia) with the dose of 40 mg q8hours. Treatment in both groups will continue for 7 days.
ANRS, Emerging Infectious Diseases. NCT04920838, first registered 10 June 2021	RCT with parallel assignment	600	Patients will be randomised to receive Tablets containing 500 mg of paracetamol. One to two tablets every 4-6 hours as required, to a maximum of 6 tablets (3 grams) daily in divided doses or Inhaled Ciclésonide: 320 mcg BID per day and Oral Nitazoxanide:2000 mg tablets daily (divided into two daily intakes of two tablets of nitazoxanide 500 mg) during 14 days or telmisartan (Micardis® 20 mg) during 10 days

Table 4: Summary of findings

Author(s): A Hohlfeld, S Ebrahim, T Kredo, R de Waal, A Gray

Question: Should inhaled corticosteroids be used to treat patients with suspected or confirmed COVID-19 not requiring oxygen therapy in hospital or ambulatory settings?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS	Standard care	Relative (95% CI)	Absolute (95% CI)	
5	RCTs	serious[a]	serious[b]	not serious[c]	serious[d]	none	770/1533 (50.2%)	669/2445 (27.4%)	**RR 1.28** (0.87 to 1.88)	**77 more per 1,000** (from 36 fewer to 241 more)	⊕◯◯◯ Very low
2	RCTs	serious[a]	serious[b]	not serious	serious[e]	none	183	180	-	mean **2.74 days fewer** (5.47 fewer to 0.01 fewer)	⊕◯◯◯ Very low
6	RCTs	serious[f]	not serious	not serious[c]	serious[g]	none	102/1549 (6.6%)	156/2470 (6.3%)	**RR 0.95** (0.61 to 1.49)	**3 fewer per 1,000** (from 25 fewer to 31 more)	⊕⊕◯◯ Low
1	RCT	very serious[h]	not serious	not serious	serious[d]	none	35	26	-	mean **0.4 days fewer** (4.22 fewer to 3.42 more)	⊕◯◯◯ Very low
2	RCTs	serious[f]	not serious	not serious	serious[d]	none	52/1157 (4.5%)	75/2066 (3.6%)	**RR 1.27** (0.90 to 1.80)	**10 more per 1,000** (from 4 fewer to 29 more)	⊕⊕◯◯ Low
2	RCTs	not serious[i]	not serious	not serious	very serious[g]	none	14/1157 (1.2%)	14/2066 (0.7%)	**RR 1.79** (0.86 to 3.71)	**5 more per 1,000** (from 1 fewer to 18 more)	⊕⊕◯◯ Low
2	RCTs	serious[f]	serious[b]	not serious	very serious[g]	none	20/88 (22.7%)	14/80 (17.5%)	**RR 2.02** (0.20 to 20.39)	**179 more per 1,000** (from 140 fewer to 1,000 more)	⊕◯◯◯ Very low
4	RCTs	serious[f]	not serious	not serious	very serious[g]	none	78/488 (16.0%)	69/490 (14.1%)	**RR 1.11** (0.73 to 1.68)	**15 more per 1,000** (from 38 fewer to 96 more)	⊕◯◯◯ Very low
2	RCTs	serious[f]	not serious	not serious	very serious[g]	none	9/1155 (0.8%)	9/2066 (0.4%)	**RR 1.23** (0.48 to 3.13)	**1 more per 1,000** (from 2 fewer to 9 more)	⊕◯◯◯ Very low

CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio

Explanations

a. Downgraded by one level for Risk of Bias. Unblinded; self-reported and subjective outcomes
b. Downgraded one level for serious inconsistency: there was considerable unexplained heterogeneity.
c. Pre-hospital, UK, suspected and confirmed sars-cov-2. RCTs included vaccinated participants (Yu 2021, Duvignaud 2022)
d. Downgraded by one level for imprecision: small sample size; confidence interval crosses the null effect and includes appreciable benefit and harm
e. Downgraded by one level for imprecision: small sample size, calculated optimal information size required more than 500 participants (a mean difference of two days from ten to eight days)
f. Downgraded by one level for Risk of Bias: Unblinded participants and personnel.
g. Downgraded by two levels for imprecision: Confidence Interval is wide, includes the null effect and crossing appreciable benefit and appreciable harm
h. Downgraded by two levels for Risk of Bias: some concerns deviation from intended intervention, missing data and outcome measurement
i. Downgrading not required for Risk of Bias: low concern for this outcome found for the RCTs

Table 5: Quality appraisal: overall risk of bias for the primary outcome (2-grade increase on an ordinal scale for clinical deterioration) from Yu *et al*., 2021 (9)

Bias	Author's judgment	Support for judgment
Randomisation	 Low	Quote: "Randomized using a secure, in-house, web-based randomization system." Comment: Allocation sequence random. Allocation sequence concealed. Imbalances in baseline characteristics appear to be compatible with chance.
Deviations from intervention	 Low	Quote: "Open-label" Comment: Unblinded study (participants and personnel/carers) Deviations from intended intervention arising because of the study context: No participant cross-over. In the outpatient setting, we consider no important cointerventions of interest. Hence, no deviation arose because of the trial context. Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention. Risk assessed to be low for the outcome: Mortality (D28). Hospitalization or death. WHO score 7 and above (D28).
Missing outcome data	Some	Comment: Number of patients concurrently randomized unclear for usual care arm, 1073 randomized for treatment arm; 990 patients analyzed for treatment arm, 987 analyzed for control arm. Data not available for all or nearly all participants randomized. No evidence that the result is not biased. Reasons for missing data: not eligible (16 vs unknown); withdrew consent (10 vs unknown); recovered at day 0 (3 vs unknown); no outcome diary information (54 vs unknown) Missingness could depend on the true value of the outcome. Not likely that missingness depends on the true value of the outcome. Proportions of missing data do not correspond with the number of participants analysed in the control group. Risk assessed to be some concerns for the outcome: Mortality (D28). Hospitalization or death. WHO score 7 and above (D28).
Measurement of the outcome	 Low	Comment: Method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study (outcome assessor) Comment: Method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study (outcome assessor) **SERIOUS ADVERSE EVENTS** The authors reported on serious adverse events that may contain both clinically- and laboratory-detected outcomes which can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic. Risk assessed to be **some concerns** for the outcome: First reported recovery, time to first reported recovery, early sustained recovery, Serious adverse events. **MORTALITY** Observer-reported outcome not involving judgement. Risk assessed to be low for the outcomes: Mortality (D28). **HOSPITALIZATION OR DEATH, WHO SCORE 7 AND ABOVE** For the outcome hospitalization or death, we consider that the assessment cannot possibly be influenced by knowledge of intervention assignment. Risk assessed to be low for the outcome: Hospitalization or death. WHO score 7 and above (D28)
Selection of the reported results	 Low	Comment: The protocol and statistical analysis plan (retrospective, dated 22nd February, 2021) and registries (prospective, dated 25th and 22nd March, 2020) were available. Results were not selected from multiple outcome measurements or analyses of the data. Trial analyzed as pre-specified. Risk assessed to be low for the outcome: Mortality (D28). Hospitalization or death. WHO score 7 and above (D28).
Overall risk of bias	Some	

Table 6: Quality appraisal: overall risk of bias for the primary outcome (2-grade increase on an ordinal scale for clinical deterioration) from Ramakrishnan *et al.*, 2021 (10)

Bias	Author's judgment	Support for judgment
Randomisation	Some	Quote: "The randomisation sequence was created using a random number generation function and allocation to each group was done through block randomisation in a 1:1 ratio." Comment: Allocation sequence random. Unclear if allocation sequence concealed. Imbalances in baseline characteristics appear to be compatible with chance.
Deviations from intervention	Some	Quote: "Open-label" Comment: Unblinded study (participants and personnel/carers) Deviations from intended intervention arising because of the study context: No participant cross-over. No information on administration of co-interventions of interest: Biologics, antivirals and corticosteroids. Hence, no information on whether deviations arose because of the trial context. Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention. Per protocol for resolution of symptoms, which is not an appropriate method Risk assessed to be some concerns for the outcome: Hospitalization or death. Serious adverse events. Resolution of symptoms
Missing outcome data	Some	Data available for all participants Risk assessed to be some concerns for the outcome: Hospitalization or death. Serious adverse events. Resolution of symptoms
Measurement of the outcome	Low	Comment: Method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study (outcome assessor) **SERIOUS ADVERSE EVENTS** The authors reported on serious adverse events that may contain both clinically- and laboratory-detected outcomes which can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic. Risk assessed to be **some concerns** for the outcome: First reported recovery, time to first reported recovery, early sustained recovery, Serious adverse events. **HOSPITALIZATION OR DEATH** For the outcome hospitalization or death, we consider that the assessment cannot possibly be influenced by knowledge of intervention assignment. Risk assessed to be **low for the outcome**: Hospitalization or death, oxygen administration, mechanical ventilation, ICU admission.
Selection of the reported results	Low	Comment: The protocol, statistical analysis plan and registries were available. Results were not selected from multiple outcome measurements or analyses of the data. Trial analyzed as pre-specified. Risk assessed to be low for the outcome: Hospitalization or death. Serious adverse events.
Overall risk of bias	Some	

Table 7: Quality appraisal: overall risk of bias for the primary outcome (2-grade increase on an ordinal scale for clinical deterioration) from Clemency et al., 2021 (11)

Bias	Author's judgment	Support for judgment
Randomisation	Low	Quote: "The randomization schedule was generated by the contract manufacturing organization and incorporated into the labeling of kits. MDI kits were sent to the study sites in blocks of 6 with 3 active and 3 placebo kits randomized within each block. Individual site personnel dispensed individual kits in order, blinded to the assignment." Comment: Allocation sequence random. Allocation sequence probably concealed. Imbalances in baseline characteristics appear to be compatible with chance.
Deviations from intervention	Low	Quote: "Double blind" Comment: Blinded study (participants and personnel/carers) Our analysis for the binary outcomes is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

		Risk assessed to be low for the outcomes: Mortality (D28). Mortality (D60 or more). Hospitalization or death. Adverse events.
Missing outcome data	Some	Comment: 400 participants randomized; 400 participants analyzed. Data not available for all or nearly all participants randomized. No evidence that the result is not biased. Reasons: 11 vs 9 were lost to follow up, 5 vs 4 withdrawal by patient, 2 vs 7 had an AE with hospitalization, 1 vs 1 had an AE without hospitalization and 0 vs 1 discontinued at the physician discretion. Missingness could depend on the true value of the outcome. Not likely that missingness depended on the true value of the outcome (similar reasons and proportions of missingness between arms). Risk assessed to be some concerns for the outcomes: Mortality (D28). Mortality (D60 or more). Hospitalization or death. Adverse events.
Measurement of the outcome	Low	Comment: Method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Blinded study (outcome assessor). Risk assessed to be low for the outcomes: Mortality (D28). Mortality (D60 or more). Hospitalization or death. Adverse events.
Selection of the reported results	Low	Comment: The protocol, statistical analysis plan, and registry were available (May 6th 2020). Outcomes pre-specified. Results were not selected from multiple outcome measurements or analyses of the data. Trial analyzed as pre-specified. Risk assessed to be low for the outcomes: Mortality (D28). Mortality (D60 or more). Hospitalization or death. Adverse events.
Overall risk of bias	Some	

Table 8: Quality appraisal: overall risk of bias for the primary outcome (2-grade increase on an ordinal scale for clinical deterioration) from Alsultan et al., 2021 (12)

Bias	Author's judgment	Support for judgment
Randomisation	Some	Quote:"49 patients were included in this randomized control trail by randomized number tables after excluding ineligible patients." Comment: Allocation sequence random. Unclear allocation concealment.
Deviations from intervention	Low	Quote: "This study had some limitations, such as lack of blinding and reduced number of participants in a single isolation ward." Comment: Unblinded study (participants and personnel/carers) Deviations from intended intervention arising because of the study context: No participant cross-over. Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention. Risk assessed to be low for the outcome: Hospitalization or death.
Missing outcome data	Low	Table 4 indicates that data available for all participants No evidence that the result is not biased. Missingness could depend on the true value of the outcome. Not likely that missingness depends on the true value of the outcome.
Measurement of the outcome	Low	Comment: Method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study (outcome assessor) **MORTALITY** Observer-reported outcome not involving judgement. Risk assessed to be low for the outcomes: Mortality **HOSPITALIZATION OR DEATH, WHO SCORE 7 AND ABOVE** For the outcome hospitalization or death, we consider that the assessment cannot possibly be influenced by knowledge of intervention assignment. Risk assessed to be low for the outcome: Hospitalization or death Difficult for an assessor to make a decision on hsopitalisation based on knowing what the participant's intervention arm. Similarly, knowing the intervention arm should not determine the length of hospital stay

Selection of the reported results	Some	No protocol or trial registration noted
Overall risk of bias	Some	

Table 9: Quality appraisal: overall risk of bias for the primary outcome (2-grade increase on an ordinal scale for clinical deterioration) from Song et al., 2021 (13)

Bias	Author's judgment	Support for judgment
Randomisation	Some	Quote:"computer-generated variable blocks ranging from 4 to 8 patients per each center, and the code numbers for eligible patients were assigned in ascending sequential order." Comment: Allocation sequence random. Unclear allocation concealment.
Deviations from intervention	Some	Quote: "Open-label" Comment: Unblinded study (participants and personnel/carers) Deviations from intended intervention arising because of the study context: No participant cross-over. No information on administration of co-interventions of interest: biologics. Antivirals and corticosteroids were reported During the trial period, evidence of the ineffectiveness of hydroxychloroquine was published and a third ciclesonide plus hydroxychloroquine arm was combined with the ciclesonide alone arm. Eight patients in the ciclesonide group received oral HCQ treatment concomitantly for 10 days. Clinical failure was defined as the case of clinical deterioration requiring high-flow nasal oxygen or mechanical ventilation, resulting in salvage treatment with dexamethasone and remdesivir. 1/35 in the treatment arm and 5/26 in the SOC arm reached this endpoint. These deviations were not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. **MORTALITY, SERIOUS ADVERSE EVENTS** Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention. Risk assessed to be some concerns for the outcomes: Mortality (D28). Incidence of viral negative conversion (D7). Serious adverse events. **VIRAL NEGATIVE CONVERSION** Participants were analyzed according to their randomized groups for the outcome. Of note, 12 participants were excluded from the analysis post-randomization, of which 2 were due to reasons other than missing data (issues with eligibility criteria). The remaining 10 were due to missing data and is accounted for in domain 3. This method was considered appropriate to estimate the effect of assignment to intervention for this outcome. Risk assessed to be some concerns for the outcomes: Incidence of viral negative conversion (D7).
Missing outcome data		Comment: 68 participants randomized, 61 participants analyzed for mortality and serious adverse events, 56 participants analyzed for viral negative conversion. **MORTALITY, SERIOUS ADVERSE EVENTS** Data not available for all or nearly all participants randomized. No evidence that the result is not biased. Reasons: 7 participants were excluded from the analyses because of issues with eligibility criteria (2 participants), withdrawal of consent (3 participants), or transfer to other hospitals within 3 days after study enrollment (2 participants). It is not clear which arms they were from. Missingness could depend on the true value of the outcome. No information on whether missingness is likely to depend on the true value of the outcome (but randomization is 1:1 and the number analyzed is 35 vs 26 hence it is more likely that there is an uneven proportion of missingness between arms). Risk assessed to be high for the outcomes: Mortality (D28). Serious adverse events. **VIRAL NEGATIVE CONVERSION** Data not available for all or nearly all participants randomized.

		No evidence that the result is not biased. Reasons: 7 participants were excluded from the analyses because of issues with eligibility criteria (2 participants; accounted for in domain 2), withdrawal of consent (3 participants), or transfer to other hospitals within 3 days after study enrollment (2 participants). It is not clear which arms they were from. A further 1 vs 4 in the SOC arm were not included due to prior clinical progression. Missingness could depend on the true value of the outcome. No information on whether missingness is likely to depend on the true value of the outcome (but perhaps uneven proportion of missingness between arms based on 1 vs 4 clinical progression exclusion; also randomization is 1:1 and the number analyzed is 34 vs 22 hence it is more likely that there is an uneven proportion of missingness between arms). Risk assessed to be high for the outcome: Incidence of viral negative conversion (D7).
Measurement of the outcome	 Some	Comment: Method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study (outcome assessor) **MORTALITY, VIRAL NEGATIVE CONVERSION** Observer-reported outcome not involving judgement. Risk assessed to be low for the outcomes: Mortality (D28). Incidence of viral negative conversion (D7). **SERIOUS ADVERSE EVENTS** The authors reported on adverse events and serious adverse events that may contain both clinically- and laboratory-detected events, which can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic. Risk assessed to be some concerns for the outcomes: Serious adverse events.
Selection of the reported results	 Low	Comment: The registry was available dated June 24, 2021 **VIRAL NEGATIVE CONVERSION, SERIOUS ADVERSE EVENTS** Outcome pre-specified. Results were not selected from multiple outcome measurements or analyses of the data. Trial analyzed as pre-specified. Risk assessed to be low for the outcome: Incidence of viral conversion (D7). Serious adverse events. **MORTALITY** Mortality outcome was not pre-specified in the registry, however, we do not consider the reporting of this outcome to be selective since mortality should be reported even if not planned. Results were probably not selected from multiple outcome measurements or analyses of the data. Trial analyzed as pre-specified. Risk assessed to be low for the outcome: Mortality (D28).
Overall risk of bias	 High	

Table 10: Quality appraisal: overall risk of bias for the primary outcome (2-grade increase on an ordinal scale for clinical deterioration) from Ezer et al., 2021 (14)

Bias	Author's judgment	Support for judgment
Randomisation	 Low	Quote: "Randomisation was done centrally at the research pharmacy of the McGill University Health Centre in Montreal, Canada. The trial statistician generated a permuted block randomisation sequence using variably sized blocks of 2, 4, 6, and 8, with stratification according to sex. An unblinded research assistant sequentially assigned participants. The assignments were concealed from investigators and participants; only pharmacies and a central research assistant had access to the treatment allocation." Comment: Allocation sequence random. Allocation sequence concealed.
Deviations from intervention	 Low	Quote: "double-blinded; Investigators, participants, and statisticians were blinded to treatment allocation." Comment: Blinded study (participants and personnel/carers) Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention. Risk assessed to be low for the outcomes: Hospitalization or death. Mortality (D28). Adverse events. Serious adverse events.
Missing outcome data	 Some	Comment: 215 participants randomized; 203 participants analyzed for hospitalization and death, and 209 participants analyzed for safety.

		HOSPITALIZATION OR DEATH. MORTALITY. Data not available for all or nearly all participants randomized. No evidence that the result is not biased. Reasons: discontinuation of treatment (treatment= 1, placebo = 3), lost to follow up (1, 3), withdrew (0, 3), took an off-label inhaled steroid (1, 0). Missingness could depend on the true value of the outcome. Not likely that missingness depended on the true value of the outcome. Risk assessed to be some concerns for the outcomes: Hospitalization or death. Mortality (D28). **ADVERSE AND SERIOUS ADVERSE EVENTS.** Data available for all or nearly all participants randomized. Risk assessed to be low for the outcomes: Adverse events. Serious adverse events.
Measurement of the outcome	Low	Comment: Method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Blinded study (outcome assessor). Risk assessed to be low for the outcomes: Hospitalization or death. Mortality (D28). Adverse events. Serious adverse events.
Selection of the reported results	Low	Comment: The registry was available (dated June 17, 2020). Outcomes pre-specified. Results were not selected from multiple outcome measurements or analyses of the data. Trial analyzed as pre-specified. Risk assessed to be low for the outcome: Hospitalization or death. Mortality (D28). Adverse events. Serious adverse events.
Overall risk of bias	Some	

Table 12: Quality appraisal: overall risk of bias for the primary outcome (2-grade increase on an ordinal scale for clinical deterioration) from Duvignaud et al., 2021 (15)

Bias	Author's judgment	Support for judgment
Randomisation	Low	Quote: "Participants who meet all the inclusion criteria and none of the exclusion criteria are randomly assigned 1:1 to one of the trial arms, using a secure on-line system. The randomisation list has balanced blocks of fixed size and is stratified by study region." Comment: Allocation sequence random Allocation sequence concealed
Deviations from intervention	Low	Quote: "Open label. The allocated treatment is not masked from participants or investigators." Comment: Unblinded study (participants and personnel/carers) Deviations from intended intervention arising because of the study context: No participant cross-over. In the outpatient setting, we consider no important cointerventions of interest. Hence, no deviation arose because of the trial context Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention. Risk assessed to be low for the outcomes: Hospitalization or death. Mortality (D28). Incidence of viral negative conversion (D7). WHO score 7 and above (D28). Adverse events.
Missing outcome data	Some	Comment: 217 participants randomized; 215 participants analyzed for WHO score 7 or above; 204 participants analyzed for hospitalization or death, mortality; 107 participants analyzed for viral negative conversion; 201 analyzed for safety. Data available for all or nearly all participants randomized for WHO score 7 and above. Risk assessed to be low for the outcomes: WHO score 7 and above (D28). Data not available for all or nearly all participants randomized for mortality, hospitalization or death, viral negative conversion, safety. No evidence that the result is not biased. Missingness could depend on the true value of the outcome. Not likely that missingness depended on the true value of the outcome due to similar proportions of missing data between arms. Risk assessed to be some concerns for the outcomes: Hospitalization or death. Mortality (D28).Incidence of viral negative conversion (D7). Adverse events.
Measurement of the outcome	Some	Comment: Method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study (outcome assessor) OR Unclear blinding (outcome assessor).

		MORTALITY, VIRAL NEGATIVE CONVERSION Observer-reported outcome not involving judgement. Risk assessed to be low for the outcomes: Mortality (D28). Incidence of viral negative conversion (D7). **HOSPITALIZATION OR DEATH, WHO SCORE 7 AND ABOVE** For this outcome, we consider that the assessment cannot possibly be influenced by knowledge of intervention assignment. Risk assessed to be low for the outcomes: Hospitalization or death. WHO score 7 and above (D28). **ADVERSE AND SERIOUS ADVERSE EVENTS.** The authors reported on adverse events and serious adverse events that may contain both clinically- and laboratory-detected events, which can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic. Risk assessed to be some concerns for the outcomes: Adverse events.
Selection of the reported results	 Low	Comment: The protocol, statistical analysis plan, and prospective registry were available. Outcome pre-specified. Results were not selected from multiple outcome measurements or analyses of the data. Trial analyzed as pre-specified. Risk assessed to be low for the outcome: Hospitalization or death. Mortality (D28). Incidence of viral negative conversion (D7). WHO score 7 and above (D28). Adverse events.
Overall risk of bias	 Some	

Appendix 1: Search strategy

Epistemonikos

(title:(Coronaviridae OR coronaviridae OR coronaviridae OR coronaviridae OR coronavirinae OR "coronavirus infection" OR "2019 nCoV" OR 2019nCoV OR "2019-novel CoV" OR coronavir* OR "corona virus*" OR "middle east respiratory syndrome*" OR MERS OR "severe acute respiratory syndrome*" OR sars* OR "COVID 19" OR COVID19 OR "COVID 2019" OR "nCov 2019" OR "nCov 19") OR abstract:(Coronaviridae OR coronaviridae OR coronaviridae OR coronaviridae OR coronavirinae OR "coronavirus infection" OR "2019 nCoV" OR 2019nCoV OR "2019-novel CoV" OR coronavir* OR "corona virus*" OR "middle east respiratory syndrome*" OR MERS OR "severe acute respiratory syndrome*" OR sars* OR "COVID 19" OR COVID19 OR "COVID 2019" OR "nCov 2019" OR "nCov 19")) AND (title:("inhaled corticosteroid*" OR beclometasone OR budesonide OR flunisolide OR betamethasone OR fluticasone OR triamcinolone OR mometasone OR ciclesonide OR "fluticasone furoate") OR abstract:("inhaled corticosteroid*" OR beclometasone OR budesonide OR flunisolide OR betamethasone OR fluticasone OR triamcinolone OR mometasone OR ciclesonide OR "fluticasone furoate"))

Records retrieved: 89

Cochrane COVID Study Register

Searched the register for following individual terms with "Interventional" filter:
"inhaled corticosteroid*"
beclometasone
budesonide
flunisolide
betamethasone
fluticasone
triamcinolone
mometasone
ciclesonide
"fluticasone furoate"

Records retrieved: 32

www.covid-nma.com

Searched the register for following individual terms:
"inhaled corticosteroid*"
beclometasone
budesonide
flunisolide
betamethasone
fluticasone
triamcinolone
mometasone
ciclesonide
"fluticasone furoate"

Records retrieved: 22

PubMed

Search	Query	Results
#5	Search: **#1 AND #2** Filters: **Humans, from 2019/11/1 - 2021/7/1**	95
#4	Search: **#1 AND #2** Filters: **from 2019/11/1 - 2021/7/1**	163
#3	Search: **#1 AND #2**	168

#2	Search: "coronaviridae"[MeSH Terms] OR "coronaviridae"[All Fields] OR "coronaviridae"[MeSH Terms] OR "coronaviridae"[All Fields] OR "coronavirinae"[All Fields] OR "coronavirus infection"[All Fields] OR "2019 nCoV"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR "2019-novel CoV"[Title/Abstract] OR "coronavir*"[Title/Abstract] OR "corona virus*"[Title/Abstract] OR "middle east respiratory syndrome*"[Title/Abstract] OR "MERS"[Title/Abstract] OR "severe acute respiratory syndrome*"[Title/Abstract] OR "sars*"[Title/Abstract] OR "COVID 19"[All Fields] OR "COVID19"[Title/Abstract] OR "COVID 2019"[Title/Abstract] OR "nCov 2019"[Title/Abstract] OR "nCov 19"[Title/Abstract]	169,909
#1	Search: "inhaled corticosteroid*"[Title/Abstract] OR beclometasone OR budesonide OR flunisolide OR betamethasone OR fluticasone OR triamcinolone OR mometasone OR ciclesonide OR "fluticasone furoate"[Title/Abstract]	42,240

Appendix 2: Evidence to decision framework

Desirable Effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o Moderate o Large o Varies **X Don't know**	The demonstrated benefit is limited to a reduction in the time to self-reported resolution of symptoms, which is subjective. There are no data on quality of life (rigorously measured) or return to work/normal functioning. Self-reported resolution of symptoms would not be expected to affect the duration of self-isolation for patients with mild/moderate COVID-19. There was no significant effect on the more important clinical endpoints of reduced hospitalisation, need for oxygen therapy, progression to mechanical ventilation or death. Refer to Summary of findings table (Table 4, above).	

Undesirable Effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small o Trivial o Varies **X Don't know**	Although PRINCIPLE reported few serious adverse events, the reliance on self-report by ambulant patients meant that relevant adverse effects, such as the impact on viral shedding, could not be determined. In addition, although the duration of budesonide use was limited, an impact on immune function could not be ruled out	

Certainty of evidence: What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very Low **X Low** o Moderate o High o No included studies	<u>Resolution of symptoms (follow up: 28 days):</u> Low certainty of limited benefits - the outcome is self-reported and subject to serious risk of bias, as the studies were not blinded. <u>Hospitalisation/death (follow up: 28 days):</u> Low certainty of evidence. Both RCTs were underpowered as they terminated recruitment early.	

Values: Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability o Possibly important uncertainty or variability **X Probably no important uncertainty or variability** o No important uncertainty or variability	Although no local data are available, time to recovery may well be an important outcome for patients who are concerned about the symptoms of COVID-19.	

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison **X Probably favors the comparison** oDoes not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know	Given the uncertainty about safety, and the modest benefits, the balance of benefits and harms is uncertain.	

Resources required: How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs **X Moderate costs** o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	**Price of medicines (currently available on SA market):** *Treatment regimen:* 800 mcg 12 hourly x 14 days **Medicine** / **Price (ZAR)*** Budesonide 100mcg/dose, turbuhaler, 200 dose — R121.39 Budesonide 200mcg/dose, turbuhaler, 200 dose — R121.39 Budesonide 100mcg/dose, MDI, 300 dose — R182.09 Budesonide 200mcg/dose, MDI, 300 dose — R182.09 *SEP database, 28 December 2020; MDI=metered dose inhaler	

	Additional resources: Currently budesonide is not procured in the public sector as a stand-alone inhaler (but only as a combined budesonide/formoterol product). Whether beclomethasone (200mcg; 200 dose, R73.26, as per HP07-2020DAI/01) is a viable alternative is uncertain. • Other concerns include the limited national supply which would impact negatively on the availability of inhaled corticosteroids for patients with asthma or chronic obstructive pulmonary disease.	

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies **X No included studies**	There were no included studies that addressed cost effectiveness.	

Equity: What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced **X Probably no impact** o Probably increased o Increased o Varies o Don't know	Potentially, this option could, if adopted, impact negatively on the availability of inhaled corticosteroids for patients with asthma or chronic obstructive pulmonary disease.	

Acceptability: Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no **X Probably yes** o Yes o Varies o Don't know	No local survey data is available, but the Committee considered that this may also be a very attractive option for primary care providers, who are aware of the paucity of treatment options for ambulant patients not requiring oxygen therapy.	

Feasibility: Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no **X Probably yes** o Yes o Varies o Don't know	The provision of inhaled budesonide to all ambulant patients, or only to those aged ≥65 years or ≥50 years with co-morbidities, with confirmed COVID-19 is feasible, but would represent a considerable expenditure for uncertain benefits.	

Appendix 3: Updating of rapid report

Date	Signal	Rationale
25 March 2022	Published Cochrane review of inhaled corticosteroids for the treatment of COVID-19, March 2022	Systematic review of 3 RCTs (search was conducted up to 7 October 2021).

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	9 July 2021	AH, VN, TK, AG, RdW	Inhaled corticosteroids are not recommended for routine use in ambulant or hospitalised patients with COVID-19. Modest benefit of self-reported improvement of symptoms (low certainty), with high cost.
Second	6 June 2022	AH, SE, TK, AG, RdW	No change to the recommendation and the rationale.

For internal NDoH use:
WHO INN: Corticosteroids
ATC: R01AD
ICD10: U07.1/U07.2