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: 9 July 2021

Key findings

- We conducted a rapid review of evidence for the use of inhaled corticosteroids in ambulatory and hospitalised patients with COVID-19, not requiring oxygen therapy.
- We identified 2 randomised controlled trials (RCTs) in adults that compared inhaled budesonide to standard of care, in ambulatory care. Both RCTs were stopped early after interim analyses showed significant effects on time to symptom resolution. The largest trial included patients ≥65 years old or ≥50 years old with at least one co-morbidity; the other RCT included adults >18 years.
- There was no significant difference in the composite outcome of hospitalisation or death by 28 days (relative risk (RR) 0.44, 95% confidence interval (CI) 0.11 to 1.84), based on 2 RCTs, with 2252 participants; low certainty evidence.
- There were no significant differences in progression to requiring oxygen (RR 0.70, 95% CI 0.48 to 1.03) or progression to requiring mechanical ventilation (RR 1.05, 95% CI 0.46 to 2.40), based on 1 RCT, with 2112 participants; low certainty evidence.
- Budesonide was associated with a small increase in the proportion of patients with self-reported resolution of symptoms by 28 days (RR 1.11, 95% CI 1.04 to 1.18; number needed to treat (NNT) 15 (95% CI 9 to 40), based on 2 RCTs (2252 participants); low certainty evidence. One RCT (2112 participants) showed that the time to self-reported resolution of symptoms was shorter in those on budesonide (median 2.6 days, interquartile range (IQR) 1.0 to 4.7); moderate certainty evidence.
- Neither of the 2 RCTs reported all possible adverse events. Based on 1 RCT (2112 participants), budesonide was associated with an increased risk of serious adverse events (RR 5.23, 95% CI 0.25 to 108.86); very low certainty evidence. This was based on only 2 non-COVID-related hospitalisations. However, the impact of increased use of inhaled corticosteroids on viral shedding and immune function in ambulant patients has been poorly described.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: The 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 availability of inhaled corticosteroids for use by patients with asthma or chronic obstructive pulmonary disease.
Level of Evidence: Low certainty 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)

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

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

BACKGROUND

Inhaled corticosteroids 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 an ambulatory setting?

METHODS

A rapid review of the evidence was conducted by searching selected electronic databases (PubMed, Epistemonikos, the Cochrane COVID Register and www.covid-nma.com) on 17 June 2021. 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. 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 all outcomes, except serious adverse events (SAEs) (4). For SAEs, the reviewers relied upon the risk of bias assessment provided by the COVID-NMA living systematic review(5). 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 difference 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 reactions. Serious adverse events

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

RESULTS

Results of the search

The 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) (8, 9). A total of 17 ongoing clinical trials were identified. Table 1 shows the main characteristics and outcomes of the included trials. Table 2 describes the excluded studies and Table 3 summarises the ongoing trials.

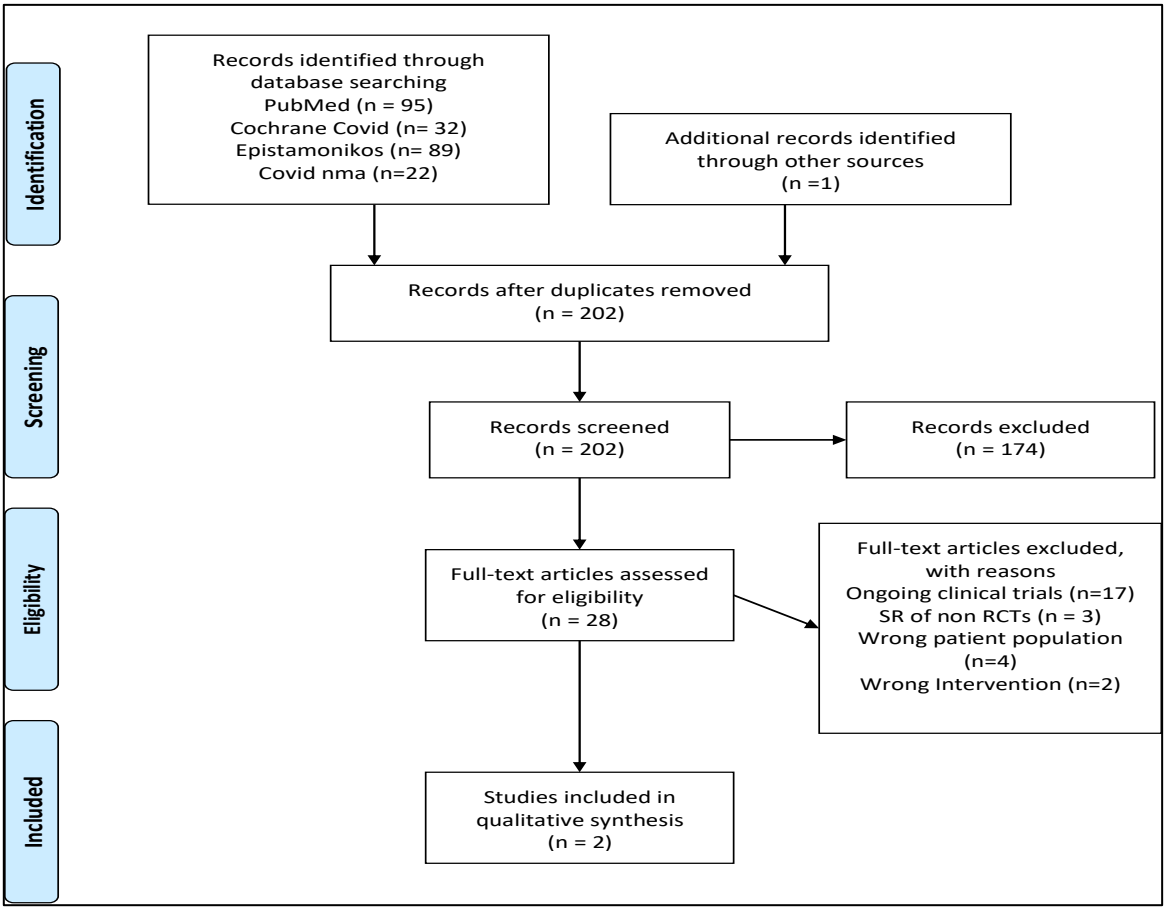

Figure 1. PRISMA flow diagramme for review

Description of included studies

We included two RCTs, the PRINCIPLE trial (Yu *et al*. 2021)(8) and the STOIC trial (Ramakrishnan *et al*. 2021)(9), both of which investigated inhaled budesonide in ambulant patients. No direct evidence for the population of hospitalised patients not requiring oxygen therapy is therefore available.

The PRINCIPLE trial randomised ambulatory patients with suspected or confirmed COVID-19 and aged either ≥65 years or ≥50 years with co-morbidities, to inhaled budesonide, standard of care, or other treatments. This formed part of a prospective adaptive platform randomised trial. Study results were published as a pre-print in April 2021 after randomisation was stopped because interim analysis showed a statistically significant effect on time to self-reported recovery. The authors initially estimated that approximately 1500 participants were required per arm to provide 90% power of detecting a 50% reduction in the primary outcome, which was the relative risk of hospitalisation and/or death at 28 days, assuming a hospitalisation rate of 5%. However, during the study the investigators noted a marked decrease in hospital admissions attributable to the United Kingdom lockdown and vaccination program. They therefore added a co-primary outcome of time to self-reported recovery. By the time randomisation was stopped, 1032 participants had been randomised to inhaled budesonide, 1943 to usual care (1080 of whom were randomised at the time that budesonide was available in the trial: the 'concurrent randomisation population'), and 1688 to other treatments. Results were reported for those randomised to budesonide and usual care only, restricted to the concurrent randomisation population. Further, at the time of publication, some participants had not yet completed the 28-day follow-up period. Critically, this RCT's interim analysis is therefore not powered for the initial primary outcome of COVID-19 related hospital admission and/or death. (8).

The STOIC trial randomised adults ≥18 years with mild COVID-19 symptoms to inhaled budesonide or standard of care. The study was also stopped early, after investigators requested an unplanned interim analysis, because of reduced rates of recruitment. The reduced recruitment was attributed to the lockdown in place in the United Kingdom, vaccination, and recruitment to the PRINCIPLE study. The study intended to recruit 199 participants in each arm, to provide 80% power to detect a 50% reduction in the primary outcome of urgent care visits or hospitalisation, based on

the assumption that 20% of all COVID-19 cases were severe and would require hospitalisation. (10, 11). At the time of the interim analysis, the trial had only recruited 73 participants in each arm. An independent statistical review established that with further participant enrolment, the study results would not change (9).

Effects of the intervention

All results are presented for inhaled budesonide compared to standard of care, in those with suspected or confirmed COVID-19. Table 4 summarises the evidence profiles for the results. Table 5 depicts the quality appraisal of the two included RCTs.

Efficacy outcomes:

Resolution of symptoms
Two RCTs reported the proportion of participants with self-reported resolution of symptoms. The PRINCIPLE trial reported at 28 days and STOIC trial reported at 14 days. ICS probably results in a slight increase in the proportion of patients reporting resolution of symptoms (RR 1.11, 95% CI 1.04 to 1.18; I^2= 0; 2252 participants; moderate certainty evidence). This represents 68 more patients reporting resolution of symptoms per 1000 patients with suspected or confirmed COVID-19 (95% CI: 25 more to 112 more) treated with inhaled budesonide compared with standard of care.

Time to resolution of symptoms
One RCT reported time to self-reported resolution of symptoms. The PRINCIPLE trial reported that inhaled budesonide results in a modest reduction in time to resolution of symptoms (median 2.59 [IQR 0.956 - 4.714] days; 2975 participants; moderate certainty evidence), based on a Bayesian piecewise exponential model adjusted for age and comorbidity at baseline, with a 95% Bayesian credible interval.

Progression to hospitalisation
Two RCTs reported progression to hospitalisation and death as a composite outcome. Inhaled budesonide may result in little to no difference in the risk of hospitalisation or death (RR 0.44, 95% CI 0.11 to 1.84; I^2=74%; 2252 participants; low certainty evidence). This represents 50 fewer hospitalisations or deaths per 1000 patients with suspected or confirmed COVID-19 (95% CI: 79 fewer to 75 more) treated with inhaled budesonide compared with standard of care.

Duration of hospitalisation
Neither of the RCTs reported on this outcome.

Progression to requiring oxygen
One RCT reported progression to requiring oxygenation by 28 days. Inhaled budesonide may result in little to no difference in progression to requiring oxygen (RR 0.70; 95% CI 0.48 to 1.03; 2115 participants; low certainty evidence). This represents 18 fewer requiring oxygen per 1000 patients with suspected or confirmed COVID-19 (95% CI: 31 fewer to 2 more) treated with inhaled budesonide compared with standard of care.

Progression to requiring mechanical ventilation
One RCT reported progression to requiring mechanical by 28 days. Inhaled budesonide may result in little to no difference in progression to requiring mechanical ventilation (RR 1.05; 95% CI 0.46 to 2.40; 2115 participants; low certainty evidence). This represents 1 more patient requiring mechanical ventilation per 1000 patients with suspected or confirmed COVID-19 (95% CI: 6 fewer to 14 more) treated with inhaled budesonide compared with standard of care.

Proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis
Neither of the RCTs reported on this outcome.

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

Safety outcomes:
Adverse events
In the STOIC trial five participants from the ICS group reported adverse events, four had sore throat and one had

dizziness. The relative risk of adverse events was this estimated as 10.69 (95% CI: 0.60 to 189.81), but assessed as very low certainty evidence.

Adverse reactions
Neither of the RCTs reported on this outcome

Serious adverse events
In the PRINCIPLE trial two participants from the ICS group reported hospitalisations unrelated to COVID-19, which would have been reported as severe adverse events (SAEs). The relative risk of SAEs was this estimated as 5.23 (95% CI: 0.25 to 108.86), but assessed as very low certainty evidence.

CONCLUSION

Budesonide has not been shown to have a significant impact on hospitalisation or mortality, but the two included studies were underpowered for this outcome. The majority of the evidence was obtained from the PRINCIPLE trial, which enrolled patients aged either ≥65 years or ≥50 years with co-morbidities. Budesonide was associated with a small reduction in time to self-reported recovery, but no difference in more important clinical endpoints. Adverse effects were poorly characterised.

Reviewers: Ameer Hohlfeld, Vera Ngah, Tamara Kredo, Renee de Waal, Andy Gray.

Declaration of interests: AM & TK (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. (8)	multi-centre, primary care, open-label, multi-arm, prospective adaptive platform randomised trial	Setting: UK (outpatients) n = 1032 (budesonide); 805 confirmed COVID-19 positive n = 1943 (usual care alone); 860 confirmed COVID-19 positive n= 1688 (other treatment groups, as part of the platform trial); no information on number of confirmed COVID-19 positive Age, mean (range): 62.8 (50 – 100) years Less than 65 years: 418(40.5%)) control 1020(52.5%) Older than 65 years: intervention 614 (59.5%), control 923 (47.5%) Gender Male, n= 1376 (43.6%): (492) intervention; (884) control Comorbidities (percent): 2474 (83.2%) intervention 836 (81.0%), control 1638 (84.3%) Symptom onset, median (IQR): 6 (4 to 9) days Ethnicity: white (2649, 89%), intervention (951), control (1698), mixed background (41, 1.4%), intervention (12), control (29), black (14, 0.5%), intervention (6), control (8), South Asian (139, 4.7%), intervention (52), control (87), other (39, 0.9%), intervention (5), control (22), Smoking status: current smoker (260, 8.7%), intervention (68, 6.6%), control192 (9.9%), former smoker (1164,39.1%), intervention (420, 40.7%), control (744, 38.3%), never smoker (1487, 50.0%), intervention (529, 51.3%), control 958 (49.3%), missing (64), intervention (15, 1.5%), control (49, 2.5%) Asthma, COPD or lung disease 544 (18.3%), intervention (88, 8.5%), control (456, 23.5%); *for the concurrent randomization analysis population (pre-specified sensitivity analysis)*:* Asthma, COPD or lung disease 215 (10.2%), intervention (88, 8.5%), control (127, 11.8%). Diabetes, 609 (20.5%), intervention 202, (19.6%), control 407 (20.9%) Heart problems 457 (15.4%), intervention 173 (16.8%) control 284 (14.6%) Medication high blood pressure 1305 (43.9%), intervention 466 (45.2%), control 839 (43.2%)	**Treatment** Inhaled budesonide 800µg twice daily for 14 days Co-Intervention: Usual care Duration: 28 days **Control** Usual care alone	**Co-primary endpoints measured (within 28 days):** • **Time to first self-reported recovery** First reported recovery, n (%) for COVID-19 positive population, budesonide group compared to usual care (534/751 [71.1%] vs 666/1028 [64.7%]); Concurrent randomisation population (participants inhaled budesonide and usual care group only) budesonide group compared to usual care (703/961 [73.2%] vs 663/996 [66.6%]). Time to first reported recovery, median (IQR) for COVID-19 positive population, budesonide group compared to usual care (11 [5, 27] vs 14 [6, -]); Concurrent randomisation population budesonide group compared to usual care 10 [4, 25] vs 13 [4, -]) • **Hospitalization or death related to COVID-19** The point estimate of the proportion of COVID-19 related hospitalization/deaths within 28 days follow up was slightly lower in the budesonide group compared to usual care (59/692 [8.5%] vs 100/968 [10.3%]; Results were similar in the concurrent randomized analysis population (68/892 [7.6%] vs 91/928 [9.8%]. **Secondary outcomes[a]:** • **How well participants felt over 28 days** Early sustained recovery in budesonide group compared to usual care (221/687 [32.2%] vs 156/709 [22.0%]) Rating of how well participant feels (1 worst, 10 best), mean (SD)[n] at day 7 budesonide group compared to usual care was 7.0 (1.8) [714] vs 6.6 (1.9) [730], at day at day 14 budesonide group compared to usual care day 7.9 (1.7) [701] vs 7.5 (1.7) [723], at day 21 budesonide group compared to usual care 8.4 (1.5) [572] vs 7.9 (1.6) [568], at day 28 budesonide group compared to usual care 8.4 (1.5) [649] vs 8.2 (1.50 [662]. Well-being (WHO5 Questionnaire), mean (SD)[n] at day 14 budesonide group compared to usual care 42.6 [24.9] [673] vs 39.1 [24.6] [689], at day 28 budesonide group compared to usual care 54.9 (25.20 [612] vs 51.2 (24.9) [620]. • **Duration of severe symptoms and symptom recurrence** • **Self-reported contact with ≥1 healthcare service** In budesonide group compared to usual care (400/746 [53.6%] vs 440/763 [57.7%]) • **GP reported contact with ≥1 healthcare service** In budesonide group compared to usual care (167/344 [48.5%] vs 186/341 [54.5%]) • **Prescription of antibiotics** In budesonide group compared to usual care (31/330 [9.4%] vs 28/320 [8.8%]) • **Hospital assessment without admission**

Citation	Study design	Population (n)	Treatment	Main findings
		Liver disease 76 (2.6%), intervention22 (2.1%), control 54 (2.8%) Stroke or other neurological problem 183 (6.2%), intervention 70 (6.8%), control113 (5.8%) Taking ACE inhibitor 651 (21.9%), intervention 242 (23.4%), control 409 (21.0%) Eligibility: Suspected COVID-19 using the NHS syndromic definition, OR symptoms consistent with COVID-19* and with a positive test for SARS-CoV-2 infection within the past 14 days. Participant is aged 65 or over OR Participant is aged 18- 64, and is experiencing shortness of breath as part of COVID-19 illness OR Participant is aged 18-64 and has any of the following underlying health conditions a) Known weakened immune system due to a serious illness or medication (e.g. chemotherapy); b) Known heart disease and/or a diagnosis of high blood pressure c) Known chronic lung disease (e.g. asthma) d) Known diabetes e) Known mild hepatic impairment; f) Known stroke or neurological problem; g) Self-report obesity or body mass index ≥35 kg/m2. These symptoms may include, but are not limited to, shortness of breath, general feeling of being unwell, muscle pain, diarrhoea and vomiting. Ineligible: already taking inhaled or systemic corticosteroids, were unable to use an inhaler, or if inhaled budesonide was contraindicated. Patient currently admitted in hospital. Almost recovered (generally much improved and symptoms now mild or almost absent). Judgement of the recruiting clinician deems ineligible. Previous randomisation to an arm of the PRINCIPLE trial		In budesonide group compared to usual care (20/750 [2.7%] vs 18/771 [2.3%]) • **Oxygen Administration** In budesonide group compared to usual care (43/742 [5.8%] vs 64/764 [8.4%]) • **Mechanical ventilation** In budesonide group compared to usual care (11/743 [1.5%] vs 11/760 [1.4%]) • **ICU admission** In budesonide group compared to usual care (9/735 [1.2%] vs 17/756 [2.2%])

Citation	Study design	Population (n)	Treatment	Main findings
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. (9)	Randomised, open-label, parallel-group, phase 2 clinical trial done in the community	Setting= Oxfordshire, UK Eligibility: Adults aged older than 18 years with symptoms of COVID-19 (new onset cough and fever or anosmia, or both) within 7 days Exclusion criteria: recent use (within 7 days) of inhaled or systemic glucocorticoids or if they had a known allergy or contraindication to inhaled budesonide. 167 recruited 21 excluded 146 randomized N=70 budesonide (mean age=44years, 39 females, 31 males) N=69 usual care (mean age =46 years, 41 females, 28 males) Race or ethnicity White: Budesonide 65 (93%), usual care 64 (93%) Non-White: Budesonide 5 (7%), usual care 5 (7%) Body-mass index, kg/m: Budesonide 2 27 (4·9) usual care 26 (4·6) Number of comorbidities†: Budesonide 1 (0–2) usual care 1 (0–1) Cardiovascular disease Budesonide 6 (9%), usual care 6 (9%) Diabetes Budesonide 3 (4%), usual care 4 (6%) Past or current history of asthma Budesonide 11 (16%) usual care 10 (14%) Duration of symptoms, days†Budesonide 3 (2–5), usual care 3 (2–4) Evidence of COVID-19-positive status Budesonide 66 (94%) usual care 65 (94%)	**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	**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 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.

[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.
***** Concurrent randomized analysis (prespecified sensitivity analysis), *"defined as all participants who were eligible for budesonide and randomized to budesonide or usual care during the time period when the budesonide arm was active, important because participants already using steroid inhalers, and therefore may have had asthma or COPD, were excluded from randomization to the budesonide arm".*

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)
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	Population (n)	Treatment
McGill University Health Centre/Research Institute of the McGill University Health Centre. NCT04435795, first registered 17 June 2020	RCT with factorial assignment	215	Patients will be randomised to normal Saline intranasal BID and Placebo 3 puff MDI inhaled BIDor Intranasal ciclesonide BID 50mcg BID to each nostril and inhaled ciclesonide 600mcg BID x 14 days
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
Korea University Guro Hospital. NCT04330586, first registered 1 April 2020	RCT with parallel assignment	60	Patients will be randomised to Standard care without ciclesonide or Ciclesonide 320ug oral inhalation q12h for 14 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

Citation	Study design	Population (n)	Treatment
Covis Pharma S.â—Ž.r.l. NCT04377711, first registered 6 May 2020	RCT with parallel assignment	400	Patients will be randomised to receive Placebo matching Alvesco , twice daily for 30 days via pMDI or inhaled Alvesco (Ciclesonide) 320mcg, twice daily for 30 days via pMDI
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, V Ngah
Question: Should inhaled corticosteroids be used to treat patients with suspected or confirmed COVID-19 not requiring oxygen therapy in hospital or ambulatory settings?
Setting: United Kingdom

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)	
Resolution of symptoms (follow up: 28 days)											
2	randomised trials	serious [a]	not serious	not serious [b]	not serious	none	758/1103 (68.7%)	712/1149 (62.0%)	**RR 1.11** (1.04 to 1.18)	**68 more per 1,000** (from 25 more to 112 more)	⊕⊕◯◯ LOW
Hospitalisation/death (follow up: 28 days)											
2	randomised trials	serious [c]	not serious	not serious	serious [d]	none	70/1103 (6.3%)	102/1149 (8.9%)	**RR 0.44** (0.11 to 1.84)	**50 fewer per 1,000** (from 79 fewer to 75 more)	⊕⊕◯◯ LOW
Time to resolution of symptoms (follow up: 28 days)											
1	randomised trial	serious [c]	not serious	not serious	not serious	none	Median 2.59 (IQR 0.956 - 4.714) days				⊕⊕⊕◯ MODERATE
Progression to requiring oxygen (follow up: 28 days)											
1	randomised trial	serious [a]	not serious	not serious	serious [e]	none	43/1032 (4.2%)	64/1080 (5.9%)	**RR 0.70** (0.48 to 1.03)	**18 fewer per 1,000** (from 31 fewer to 2 more)	⊕⊕◯◯ LOW
Progression to requiring mechanical ventilation (follow up: 28 days)											
1	randomised trial	serious [a]	not serious	not serious	serious [d]	none	11/1032 (1.1%)	11/1080 (1.0%)	**RR 1.05** (0.46 to 2.40)	**1 more per 1,000** (from 6 fewer to 14 more)	⊕⊕◯◯ LOW
Proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis (follow up: 14 days)											
1							No events for this outcome reported in the Yu trial				-
Serious AEs (follow up: 28 days)											
1	randomised trial	serious [f]	not serious	not serious	very serious [g]	none	2/1032 (0.2%)	0/1080 (0.0%)	**RR 5.23** (0.25 to 108.86)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW
Adverse events (follow up: 14 days)											
1	randomised trial	serious [f]	not serious	not serious	very serious [g]	none	5/71 (7.0%)	0/69 (0.0%)	**RR 10.69** (0.60 to 189.81)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW

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

Explanations

a. Open label trial. Outcomes are subjective and self-reported. PRINCIPLE trial is a pre-print (awaiting peer-review), therefore, results may not have been reported accurately.
b. Pre-hospital study that included suspected and confirmed SARS-COV-2 participants in the United Kingdom.
c. PRINCIPLE trial has preliminary data. Therefore, attrition and reporting data (denominators) may change from the current reported analysis to the final analysis. Data not available for all or nearly all participants randomized, therefore, RoB assessed to have some concerns for outcome hospitalisation or death.
d. Confidence Intervals are wide, crossing appreciable benefit and appreciable harm.
e. Confidence Interval crosses the null and appreciable benefit.
f. Risk of bias was downgraded by 1 level as there are some concerns of deviation from intended intervention, missing data and outcome measurement.
g. Due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants.

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 (8)

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	Some concerns	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. Risk assessed to be some concerns for the outcome: Hospitalization or death. Serious adverse events.
Missing outcome data	Some concerns	Data from interim analysis in the concurrent randomized population. Comment: 2112 patients randomized; 1957 patients analyzed for Serious Adverse Events. 1820 patients analyzed for hospitalization or death. 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 (8 vs unknown); recovered at day 0 (3 vs unknown) [not true missing data]; no outcome diary information (44 vs unknown) Missingness could depend on the true value of the outcome. Not likely that missingness depends on the true value of the outcome. Proportion of missingness are not available for the standard care arm in the concurrent randomized population but available in the overall population. Reasons in the overall population were the same between arms. Risk assessed to be some concerns for the outcome: Hospitalization or death. Serious adverse events.
Measurement of the outcome	Some concerns	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 concerns	

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 (9)

Bias	Author's judgment	Support for judgment
Randomisation	Some concerns	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 concerns	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 concerns	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 concerns	

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

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: ☐ Moderate: ☐ Small: x None: ☐ **Is benefit clinically meaningful?** Yes: ☐ No: ☐ Uncertain: x	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, ventilation or death.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: ☐ Moderate: ☐ Small: x None: ☐ **Are harms clinically meaningful?** Yes: ☐ No: ☐ Uncertain: x	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.
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☐ Low: x Very low: ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	**Resolution of symptoms (follow up: 28 days):** Low certainty of limited benefits - the outcome is self-reported and subject to serious risk of bias, as the studies were not blinded. **Hospitalisation/death (follow up: 28 days):** Low certainty of evidence. Both RCTs were underpowered as they terminated recruitment early.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: ☐ Favours control: ☐ Intervention = Control *or* Uncertain: X	Given the uncertainty about safety, and the modest benefits, the balance of benefits and harms is uncertain.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: x No: ☐ Uncertain: ☐	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.
RESOURCE USE	**How large are the resource requirements?** More intensive: X Less intensive: ☐ Uncertain: ☐	**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.
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: ☐ Major: ☐ Uncertain: ☒ x **Is the option acceptable to key stakeholders?** Yes: ☒ x No: ☐ Uncertain: ☐	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. 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.
EQUITY	**Would there be an impact on health inequity?** Yes: ☐ No: ☐ Uncertain: ☒ x	Potentially, this option could, if adopted, impact negatively on the availability of inhaled corticosteroids for patients with asthma or chronic obstructive pulmonary disease.

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.