National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[E] Evidence review for inhaled budesonide

NICE guideline NG191

November 2021

Guideline version (Final)

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Objective

This evidence review aims to evaluate the clinical effectiveness of inhaled budesonide in people with COVID-19.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

What is the effectiveness and safety of inhaled budesonide for acute symptoms and complications of COVID-19?

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

Included studies

NICE's information services team identified relevant evidence through focused evidence searches up to 15 June 2021 (see appendix B for full details). The search identified 248 references. These references were screened using their titles and abstracts and 2 full text references were obtained and assessed for relevance against the criteria in the PICO. Both studies were included in the evidence review.

Results

Key results

Compared to standard care, inhaled budesonide is no better at reducing risk of hospitalisation or death in people with COVID-19.

What is the evidence informing this conclusion?

Two studies identified from the search are included in this evidence review. The 2 randomised trials compared inhaled budesonide with usual care in 3217 non-hospitalised people with mild COVID-19 (Ramakrishnan 2021 [STOIC trial] and Yu 2021 [PRINCIPLE trial]).

Publication status

All studies have been peer-reviewed.

Study characteristics

Both studies used a dosage of 800 micrograms twice daily (1600 micrograms total daily dose) of inhaled budesonide. The included studies compared inhaled budesonide to usual care which was based on advice from the UK National Health Service (NHS). The mean ages in the STOIC trial were 44 (range 19-71) years in the budesonide group and 46 (19-79) years in the usual care group. The PRINCIPLE trial restricted enrolment to a higher risk population with 39% of the participants aged between 50 and 64 years and 61% were aged over 64 years. The proportion of women ranged from 52% to 58%. Both studies were conducted in a non-hospital setting.

What are the main results?

Efficacy

In non-hospitalised adults with COVID-19 , there were no statistically significant differences for reduction of hospitalisation or death, need for mechanical ventilation, ICU admission, symptom-related outcomes or hospital assessment without admission (Yu 2021) but there was a statistically significant difference favouring inhaled budesonide for reducing need for oxygen administration, time to first reported recovery, sustained recovery (Yu 2021) and the number of COVID-19-related urgent care visits, including emergency department assessment or hospitalisation (Ramakrishnan 2021).

Safety

There was no statistically significant difference in serious adverse events (Yu 2021).

Subgroup analysis

There was insufficient detail to accurately assess subgroups of interest.

Limitations of the evidence

There were some differences in how the included studies were designed which meant that meta-analysis was not appropriate. The population inclusion criteria of the STOIC trial (Ramakrishnan 2021) was broad (symptomatic adults aged ≥ 18 years) whereas the PRINCIPLE trial (Yu 2021) was restricted to adults that were at higher risk of complications with COVID-19 (≥65 years or ≥50 years with comorbidities). This restricted population in the PRINCIPLE trial will mean that the data may not be generalisable to younger adults with or without comorbidities.

The STOIC trial was terminated early after independent statistical review. This was because recruitment was reduced after a second national lockdown came into effect in England and implementation of the COVID-19 vaccine had started. Although the STOIC trial was terminated early and did not reach its target sample size, independent statistical review concluded that the addition of more participants would not have changed the result. However, this means that it was a very small trial with few events which may limit impact on decision-making.

Risk of bias for all outcomes was rated as 'low' or 'some concerns'. Both studies were open-label studies whereby lack of blinding could introduce bias to the more subjective outcomes. Lack of blinding is less likely to introduce bias to objective outcomes such as hospitalisation or death.

All included studies were in adults, so it is not possible to say what the efficacy or safety of inhaled budesonide for treating COVID-19 is in children or young people.

See appendix E for forest plots and see appendix F for full GRADE tables.

Our confidence in the results

The majority of the evidence was rated as low to moderate quality. Outcomes that were self-reported were downgraded due to high risk of bias. Where 95% confidence intervals crossed the line of no effect, the outcome was downgraded for imprecision. The outcome for COVID-19 related urgent-care visits was downgraded due to indirectness as it was not possible to determine from the data what the nature of the visits were as it included hospitalisations as well as emergency department attendance which can lead to different outcomes for patients.

Evidence to decision

Benefits and harms

The panel considered that the clinical evidence suggests there is no statistically significant difference for the outcomes of hospitalisation and death, or need for mechanical ventilation in people having inhaled budesonide and usual care compared with usual care alone. They considered that inhaled budesonide statistically significantly reduces the need for oxygen administration compared with usual care. The panel acknowledged that the event rates for these outcomes were low. This may be explained in part by the fact that the population had mild COVID-19 that was managed in the community. The panel noted that the thresholds for starting oxygen therapy were not reported in the trials.

Time to first reported recovery (patient reported) and time to sustained recovery was statistically significantly reduced with inhaled budesonide compared with usual care. However, the panel acknowledged that corticosteroids can potentially affect wellbeing without affecting the COVID-19 disease process. There was a statistically significant reduction in the number of people who had COVID-19-related urgent care visits. There was no statistically significant difference in serious adverse events for budesonide compared with usual care. The panel also discussed that non-serious adverse events were not reported in the studies. However, they acknowledged that the side-effect profile of budesonide is well known.

Certainty of the evidence

Most of the evidence was rated as low to moderate in quality. Outcomes that were self-reported were downgraded because of high risk of bias. When 95% confidence intervals crossed the line of no effect, the outcome was downgraded for imprecision. The outcome for COVID-19-related urgent-care visits was downgraded because of indirectness. It was not possible to determine from the data what the nature of the visits were because it included hospitalisations as well as emergency department attendance. These can lead to different outcomes for people with COVID-19.

The panel discussed the limitations of the trials and noted that the STOIC trial was a small study with very few events. They also noted the trial was stopped early as a result of an independent statistical review.

Risk of bias was rated as 'low' or 'some concerns' for all outcomes in the studies. Both trials included were open-label studies. So, the lack of blinding could have introduced bias to the more subjective outcomes such as self-reported recovery, resolution of symptoms or sustained recovery. This is because people in the trials would have been aware of the treatment they were having.

The panel discussed that the PRINCIPLE trial had a restricted population of mainly older adults and had concerns about the applicability of the trial to younger people with COVID-19. The panel noted that inhalers can be difficult to use for people unfamiliar with the devices, and so the amount of budesonide inhaled may be variable, potentially affecting the results.

Values and preferences

The panel were not aware of any systematically collected data on preferences and values, but they identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for invasive mechanical ventilation, time to recovery and serious adverse events. It is likely that these outcomes would also be of similar importance to patients. In addition, other outcomes, including less serious adverse events and longer-term outcomes such as functional independence, are likely to be of particular importance to patients. These outcomes were not reported in studies.

Resources

Cost effectiveness was not assessed as part of the evidence review.

Equity

The panel discussed that not everyone will be able to use an inhaler, which could cause equity issues should inhaled budesonide be recommended for treating COVID-19 in the future.

Acceptability

The panel were not aware of any systematically collected evidence about acceptability.

Feasibility

The panel were not aware of any systematically collected evidence about feasibility.

Inhaled budesonide is not routinely used for treating COVID-19 in the UK, so the recommendation supports current practice.

Appendices

Appendix A: PICO table

PICO table

Question:

What is the effectiveness and safety of inhaled budesonide for acute symptoms and complications of COVID-19?

Criteria	**Notes**
Population	Non-hospitalised adults aged ≥18 years with symptoms from suspected or confirmed COVID-19 which started within the last 14 days. Exclusions: People who are already receiving inhaled or systemic corticosteroids or where inhaled budesonide is contraindicated.
Interventions	Inhaled budesonide
Comparators	• Standard care alone, standard care plus placebo, or placebo Note: Standard care comprises best supportive care and in certain circumstances the use of additional drugs.
Outcomes NB: Some outcomes differ from the main MAC PICO for therapeutics due to the community/non-hospitalised setting. E.g. hospitalisation is a critical outcome for this setting.	Those marked with an * are critical outcomes • All-cause mortality (n/N)* • Hospitalisation or death (composite) (n/N)* • Number of patients requiring hospitalisation (n/N)* • Number of people requiring urgent care assessment (n/N)* • Time to recovery (days)* • Number of patients experiencing one or more serious adverse events (n/N)* • IMV (number of patients requiring IMV who were not already receiving IMV at randomisation) (n/N)*

	• NIV/HFNO (number of patients requiring NIV/HFNO who were not already receiving NIV/HFNO at randomisation) (n/N • Supplemental oxygen (number of patients requiring supplemental oxygen who were not already receiving supplemental oxygen at randomisation) (n/N) • Duration of supplemental oxygen (days) • Number of patients experiencing one or more adverse events (n/N) • Number of patients who discontinued treatment due to an adverse event (n/N) • Number of patients experiencing septic shock (n/N) • Number of patients who experienced clinical recovery (resolution of symptoms or number of patients within category 1 of an ordinal scale [non-hospitalised and returned to normal life]) • Number of patients experiencing resolution of dyspnoea/breathlessness (n/N) • Number of patients who experienced clinical improvement (measured by a one or two point decrease on a 6-8 point ordinal scale, or defined as a reduction in disease severity [e.g. 'severe' to 'mild' illness]) (n/N) • Time to improvement (days) • Number of patients requiring admission to intensive care (n/N) • Virological clearance (number of patients returning a negative PCR) (n/N) • Time to deterioration (days) • Number of patients who experienced clinical deterioration (measured by a one or two point increase on a 6-8 point ordinal scale, or defined as an increase in disease severity [e.g. 'mild' to 'severe' illness]) (n/N) • Longer-term outcomes reported in the study such as functional independence The definitions of mechanical ventilation, non-invasive ventilation and other forms of respiratory support such as high flow nasal oxygen (HFNO) therapy or continuous positive airway pressure or non-invasive bilevel ventilation may differ across the

	studies. In the context of UK practice the following definitions should be considered: **Advanced respiratory support:** Invasive mechanical ventilation (any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'), bilevel positive airway pressure (BiPAP) via translaryngeal tube or tracheostomy, continuous positive airway pressure (CPAP) via translaryngeal tube, or extracorporeal respiratory support) **Non-invasive ventilation:** includes HFNO, CPAP, CPAP via tracheostomy, and non-invasive bilevel ventilation. **Low-flow oxygen supplementation:** oxygen delivered by a simple face mask or nasal canula at a flow rate usually up to 15 litres/min.
Settings	All settings
Subgroups	• Adults ≥ 50 years • Adults ≥18 to <50 years • Positive SARS-CoV-2 PCR test • Gender • Ethnic background • Pregnant women • Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity) • Time from symptom onset • Treatment with other therapeutics used for COVID-19
Study types	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If no systematic reviews or RCT evidence is available progress to: • non-randomised controlled trials • systematic reviews of non-randomised controlled trials • cohort studies

	• before and after studies • interrupted time series studies Preprints will be considered as part of the evidence review.
Countries	Any
Timepoints	From 2020 onwards
Other exclusions	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts, and narrative reviews • animal studies • editorials, letters, news items, case reports and commentaries, conference abstracts and posters • theses and dissertations
Equality issues	Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, people who are homeless, refugees, asylum seekers, migrant workers and people who are homeless.

Appendix B: Literature search strategy/Data source

Database	Platform	Segment searched	Saved search name
MEDLINE ALL	Ovid	Ovid MEDLINE(R) ALL 1946 to June 14, 2021	RG – Budesonide – Medline
Embase	Ovid	1974 to 2021 June 14	RG – Budesonide – Embase
Cochrane Library	Wiley	Cochrane Central Register of Controlled Trials Issue 4 of 12, April 2021	RG Budesonide COVID-19
Pre-prints – bioRxiv and medRxiv	RIS via EPPI	IS surveillance – pre-prints v3	

Source	No. of results	Total results	Total after deduplication
MEDLINE ALL	113	302	248
Embase	170		
Cochrane CENTRAL	4		
Pre-prints – bioRxiv and medRxiv	15		

Database search strategies

MEDLINE ALL

Database: Ovid MEDLINE(R) ALL <1946 to June 14, 2021>
Search Strategy:
---
1 SARS-CoV-2/ or COVID-19/ (85677)
2 (corona* adj1 (virus* or viral*)).ti,ab,kw,kf. (3547)
3 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab,kw,kf. (50519)
4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw,kf. (156522)
5 or/1-4 (160663)
6 limit 5 to yr="2020-Current" (147349)
7 (6 and english.lg.) not (letter or historical article or comment or editorial or news or case reports).pt. not (Animals/ not humans/) (105431)
8 Budesonide/ (4591)
9 Budes*.af. (6926)
10 (51333* or 51372* or aircort* or entocord* or D9421-C* or zentacort* or horacort* or pulmicort* or rhinocort* or acorspray* or aeron* or aerox* or allercort* or aquacort* or "b cort*" or "bebe cream*" or bidien* or bronex* or budair* or budec* or

budef* or budel* or buden* or budespray* or budiair* or budicort* or budo-san* or budon* or budosan* or bunase* or buparid* or butacort* or clebudan* or coramen* or cortiment* or cycortide* or denecort* or desona* or desonix* or dexbudesonide* or duasma* or eltair* or entocir* or entocort* or esonide* or giona* or inflammide* or inflanaze* or intesticort* or intestifalk* or jorveza* or larbex* or "map 0010*" or map0010* or miflo* or miflonid* or miflonil* or mikicort* or nebbud* or neo-rinactive* or neumocort* or novopulmon* or numark* or olfex* or ortikos* or preferid* or pregna or pulmaxan* or pulmicon* or pulmoliseflam* or pulmotide* or rafton* or respicort* or rhinosid* or ribujet* or ribuspir* or ribuvent* or "s 1320*" or s1320* or spirocort* or symbicort* or tafen* or uceris*).af. (20411)
11 8 or 9 or 10 (22646)
12 7 and 11 (110)
13 (2020-001209-22 or ISRCTN86534580).af. (1)
14 CTRI-2020-10-028581.af. (0)
15 (NCT04355637 or 2020-001616-18 or TACTIC-COVID).af. (2)
16 (NCT04361474 or 2020-001667-85 or MDL_2020_10).af. (1)
17 (NCT04416399 or 2020-001889-10).af. (2)
18 or/13-17 (5)
19 12 or 18 (113)

Embase

Database: Embase <1974 to 2021 June 14>
Search Strategy:
---
1 exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/ or experimental coronavirus disease 2019/ (125198)
2 (corona* adj1 (virus* or viral*)).ti,ab,kw. (2821)
3 (CoV not (Coefficien* or co-efficien* or covalent* or covington or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk" or CoVR or CoVS)).ti,ab,kw. (49590)
4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw. (156073)
5 or/1-4 (166860)
6 limit 5 to yr="2020-Current" (151659)
7 (6 and english.lg.) not (letter or editorial or conference).pt. not (nonhuman/ not human/) not "case report".sh. not medline*.db. (67808)
8 Budesonide/ (21841)
9 Budes*.af. (24765)
10 (51333* or 51372* or aircort* or entocord* or D9421-C* or zentacort* or horacort* or pulmicort* or rhinocort* or acorspray* or aeron* or aerox* or allercort* or aquacort* or "b cort*" or "bebe cream*" or bidien* or bronex* or budair* or budec* or budef* or budel* or buden* or budespray* or budiair* or budicort* or budo-san* or budon* or budosan* or bunase* or buparid* or butacort* or clebudan* or coramen* or cortiment* or cycortide* or denecort* or desona* or desonix* or dexbudesonide* or duasma* or eltair* or entocir* or entocort* or esonide* or giona* or inflammide* or

inflanaze* or intesticort* or intestifalk* or jorveza* or larbex* or "map 0010*" or map0010* or miflo* or miflonid* or miflonil* or mikicort* or nebbud* or neo-rinactive* or neumocort* or novopulmon* or numark* or olfex* or ortikos* or preferid* or pregna or pulmaxan* or pulmicon* or pulmoliseflam* or pulmotide* or rafton* or respicort* or rhinosid* or ribujet* or ribuspir* or ribuvent* or "s 1320*" or s1320* or spirocort* or symbicort* or tafen* or uceris*).af. (43566)
11 8 or 9 or 10 (47282)
12 7 and 11 (159)
13 (2020-001209-22 or ISRCTN86534580).af. (3)
14 CTRI-2020-10-028581.af. (0)
15 (NCT04355637 or 2020-001616-18 or TACTIC-COVID).af. (8)
16 (NCT04361474 or 2020-001667-85 or MDL_2020_10).af. (3)
17 (NCT04416399 or 2020-001889-10).af. (8)
18 or/13-17 (16)
19 12 or 18 (170)

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [SARS-CoV-2] this term only 294
#2 MeSH descriptor: [COVID-19] this term only 398
#3 (corona* near/1 (virus* or viral*)):ti,ab,kw 235
#4 (CoV NOT (Coefficien* or "co-efficient" or “co-efficiency” or “co-efficiencies” or covalent* or Covington* or covariant* or covarianc* or "cut-off value" or "cut-off values" or "cutoff value" or "cutoff values" or "cut-off volume" or "cut-off volumes" or "cutoff volume" or "cutoff volumes" or "combined optimisation value" or "combined optimisation values" or "combined optimization value" or "combined optimization values" or "central vessel trunk" or "central vessel trunks" or CoVR or CoVS)):ti,ab,kw 433
#5 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or covid19 or covid-19 or covid):ti,ab,kw 6097
#6 {or #1-#5} with Cochrane Library publication date Between Jan 2020 and Dec 2021, in Cochrane Reviews 32
#7 {or #1-#5} with Publication Year from 2020 to 2021, in Trials 5890
#8 #6 OR #7 5922
#9 MeSH descriptor: [Budesonide] this term only 1829
#10 Budes* 5128
#11 51333* or 51372* or aircort* or entocord* or "D9421-C*" or zentacort* or horacort* or pulmicort* or rhinocort* or acorspray* or aeron* or aerox* or allercort* or aquacort* or "b cort*" or "bebe cream*" or bidien* or bronex* or budair* or budec* or budef* or budel* or buden* or budespray* or budiair* or budicort* or budo-san* or budon* or budosan* or bunase* or buparid* or butacort* or clebudan* or coramen* or cortiment* or cycortide* or denecort* or desona* or desonix* or dexbudesonide* or duasma* or eltair* or entocir* or entocort* or esonide* or giona* or inflammide* or inflanaze* or intesticort* or intestifalk* or jorveza* or larbex* or "map 0010*" or map0010* or miflo* or miflonid* or miflonil* or mikicort* or nebbud* or neo-rinactive* or neumocort* or novopulmon* or numark* or olfex* or ortikos* or preferid* or pregna or pulmaxan* or pulmicon* or pulmoliseflam* or pulmotide* or rafton* or respicort* or

rhinosid* or ribujet* or ribuspir* or ribuvent* or "s 1320*" or s1320* or spirocort* or symbicort* or tafen* or uceris* 1752
#12 #9 or #10 or #11 5984
#13 #8 AND #12 15
#14 ("2020-001209-22" or ISRCTN86534580) 4
#15 (CTRI?2020?10?028581 or "CTRI-2020-10-028581" or "CTRI 2020 10 028581") 1
#16 (NCT04355637 or "2020-001616-18" or TACTIC-COVID) 1
#17 (NCT04361474 or "2020-001667-85" or MDL_2020_10) 2
#18 (NCT04416399 or "2020-001889-10") 1
#19 #14 or #15 or #15 or #17 or #18 8
#20 #13 or #19 19
#21 (clinicaltrials or trialsearch):so 367866
#22 #20 not #21 6

Pre-print sources

NOTE: these sources provide open access to preprints of preliminary reports of work that have not been peer-reviewed. They should not be relied on to guide clinical practice or health-related behaviour and should not be reported in news media as established information. All results from these sources are marked as “PRE-PRINT” at the start of the abstract in the RIS download.

Pre-print server	
Name	Pre-prints – MedRxiv and BioRxiv
URLs	https://www. MedRxiv .org/search https://www.biorxiv.org/search
MedRxiv and BioRxiv file date	IS surveillance – pre-prints v3
Search info including how the results were selected	Budesonide Budes* 51333* or 51372* or aircort* or entocord* or "D9421-C*" or zentacort* or horacort* or pulmicort* or rhinocort* or acorspray* or aeron* or aerox* or allercort* or aquacort* or "b cort*" or "bebe cream*" or bidien* or bronex* or budair* or budec* or budef* or budel* or buden* or budespray* or budiair* or budicort* or budo-san* or budon* or budosan* or bunase* or buparid* or butacort* or clebudan* or coramen* or cortiment* or cycortide* or denecort* or desona* or desonix* or dexbudesonide* or duasma* or eltair* or entocir* or entocort* or esonide* or giona* or inflammide* or inflanaze* or intesticort* or intestifalk* or jorveza* or larbex* or "map 0010*" or map0010* or miflo* or miflonid* or miflonil* or mikicort* or nebbud* or neo-rinactive* or neumocort* or novopulmon* or numark* or olfex* or ortikos* or preferid* or pregna or pulmaxan* or pulmicon* or pulmoliseflam* or pulmotide* or rafton* or respicort* or rhinosid* or ribujet* or ribuspir* or ribuvent* or "s 1320*" or s1320* or spirocort* or symbicort* or tafen* or uceris* 2020-001209-22 or ISRCTN86534580 or CTRI-2020-10-028581 or NCT04355637 or 2020-001616-18 or TACTIC-COVID or MDL_2020_10 or NCT04361474 or 2020-001667-85 or NCT04416399 or 2020-001889-10 EPPI filters: title or abstract

Number of results downloaded	15

This search was developed in compliance with section 8 of Appendix L of the NICE manual.

> NICE (15 October 2020) Developing NICE guidelines: the manual. Process and methods [PMG20]. Appendix L: Interim process and methods for guidelines developed in response to health and social care emergencies

The terms for COVID-19 were developed rapidly on Monday 16 March 2020 based on a list obtained from the Public Health England Library & Knowledge Services website. The terms were peer reviewed on Tuesday 17 March 2020 and amendments made. Further refinements were made as the pandemic developed. The following versions of the saved search strategies were used for this topic:
COVID-19-Embase-v6 Thursday 15 April 2021
COVID-19-MEDLINE-v10 Thursday 15 April 2021
COVID-19-Cochrane Strategy-v5 Friday 23rd April 2021

The virus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It causes the disease COVID-19. Coronavirus (COVID-19) is used in guidance because that is how the public are searching for it.

A new process was implemented from Monday 20 April 2020 for dealing with pre-prints from bioRxiv and medRxiv. An automated process was used to download the data from the pre-sorted COVID-19 and SARS-COV-2 collection available on the website. This RIS file was uploaded to EPPI-Reviewer and the searches were conducted using the filters, as described above. Testing was done on 16 April 2020 to show that the automatically generated content equalled the coverage of doing our own separate searches on the websites.

The Information Services team at NICE peer reviewed the principal database strategies according to the standard NICE checklist that was adapted from the 2015 Peer review of electronic search strategies (PRESS) checklist.

The search strategy was adapted from a previous strategy for a CHTE COVID-19 topic briefing on budesonide conducted in February 2021. Additional brand names and trial numbers were added to the original search.

The searches were limited to English language papers published from 2020 to current. Letters and editorial papers were removed from the strategy.

Appendix C: Included studies

Group - The PRINCIPLE Trial, Collaborative, Yu, Ly-Mee, Bafadhel, Mona 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 preprint

Ramakrishnan, Sanjay, Nicolau, Dan V Jr, Langford, Beverly et al. (2021) Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. The Lancet. Respiratory medicine

Appendix D: Evidence tables

PRINCIPLE Trial Collaborative, 2021

Bibliographic Reference	PRINCIPLE Trial Collaborative, Group; Inhaled budesonide for COVID-19 in people at higher risk in the community; 2021

Study details

Trial registration (if reported)	ISRCTN86534580
Study start date	27-Nov-2020
Study end date	31-Mar-2021
Aim of the study	To determine the effectiveness of inhaled budesonide in speeding recovery and reducing COVID-19 related hospital admission or death in people at higher risk of an adverse outcome in the community
Country/geographical location	UK
Study setting	Primary care/Community
Population description	Higher risk population with symptomatic COVID-19
Inclusion criteria	People in the community were eligible if they were aged ≥65 years, or ≥50 years with comorbidities, and had ongoing symptoms from polymerase chain reaction (PCR) confirmed or suspected COVID-19 (in accordance with the UK National Health Service definition of high temperature and/or new, continuous cough and/or change in sense of smell/taste) which had started within the previous 14 days. At the beginning of the trial, due to initial difficulties with community SARS-CoV-2 PCR testing in the UK, participants with suspected COVID-19 were included in the primary analysis population, irrespective of confirmatory testing. When

	testing became more accessible, the Trial Steering Committee recommended restricting the primary analysis population to those with confirmed COVID-19.
Exclusion criteria	People were ineligible to be randomised to budesonide if they were already taking inhaled or systemic corticosteroids, were unable to use an inhaler, or if inhaled budesonide was contraindicated
Intervention dosage (loading)	800µg twice daily
Intervention dosage (maintenance)	
Intervention scheduled duration	14 days
Intervention route of administration	Inhaler
Comparator (where applicable)	Usual care in the UK National Health Service for suspected COVID-19 in the community is largely focused on managing symptoms with antipyretics, with antibiotics only recommended if bacterial pneumonia is suspected.
Methods for population selection/allocation	Participants were randomised using a secure, in-house, web-based randomization system (Sortition).
Methods of data analysis	The first co-primary outcome, time to first self-reported recovery, was analysed using a Bayesian piecewise exponential model. The second co-primary outcome, hospitalisation/death, was analysed using a Bayesian logistic regression model. Both models were regressed on treatment group and stratification covariates (age and comorbidity). Secondary time-to-event outcomes were analysed using Cox proportional hazard models, and binary outcomes were analysed using logistic regression, adjusting for comorbidity, age, duration of illness and vaccination status.
Attrition/loss to follow-up	Budesonide: 990/1073 (92%) Ineligible n=16

	Withdrew consent/ no medical notes review n= 10 Recovered at day 0 n=3 No diary information n=54 Usual care 1858/1988 (93%) Ineligible n=8 Withdrew consent/ no medical notes review n= 21 Recovered at day 0 n=12 No diary information n=89
Source of funding	The PRINCIPLE trial is funded by a grant to the University of Oxford from UK Research and Innovation and the Department of Health and Social Care through the National Institute for Health Research as part of the UK Government's rapid research response fund.
Study limitations (Author)	An open label design was used to evaluate the addition of budesonide to usual care, rather than to assess benefit of budesonide compared to a placebo. Hospitalisations/deaths may be less influenced by placebo effects, and they found no evidence of a placebo effect in evaluations of other treatments in this trial platform
Study limitations (Reviewer)	The trial was restricted to older adults who are at higher risk for COVID-19 and therefore is partially applicable to the review as there is no data on the younger population.
Other details	The breath-actuated inhaler was chosen due to its ease of use, and was either issued by the participant's general medical practitioner, or centrally by the study team and delivered to the participant. Participants in the budesonide arm were sent a video link demonstrating inhaler use.

	Participants were followed up through an online, daily symptom diary for 28 days after randomisation, supplemented with telephone calls to non-responders on days 7, 14 and 28. The trial authors aimed to provide a self-swab for SARS-CoV-2 confirmatory PCR testing, but capacity issues early in the pandemic meant testing was unavailable for some participants.

Study arms

Inhaled budesonide (N = 833)

Usual care (N = 1126)

Characteristics

Arm-level characteristics

Characteristic	Inhaled budesonide (N = 833)	Usual care (N = 1126)
50-64 No of events	n = 297 ; % = 36	n = 475 ; % = 42
65 and over No of events	n = 536 ; % = 64	n = 651 ; % = 58
Female No of events	n = 429 ; % = 52	n = 586 ; % = 52
Male	n = 404 ; % = 48	n = 540 ; % = 48

Characteristic	Inhaled budesonide (N = 833)	Usual care (N = 1126)
No of events		
White No of events	n = 767 ; % = 92	n = 1038 ; % = 92
Mixed Background No of events	n = 9 ; % = 1	n = 5 ; % = 1
South Asian No of events	n = 43 ; % = 5	n = 64 ; % = 6
Black No of events	n = 6 ; % = 1	n = 4 ; % = 1
Other No of events	n = 8 ; % = 1	n = 14 ; % = 1
Missing No of events	n = 0 ; % = 0	n = 1 ; % = 1
Mild No of events	n = 833 ; % = 100	n = 1126 ; % = 100
Comorbidities No of events	n = 665 ; % = 80	n = 916 ; % = 80
Diabetes No of events	n = 169 ; % = 20	n = 251 ; % = 22

Characteristic	Inhaled budesonide (N = 833)	Usual care (N = 1126)
Heart problems No of events	n = 139 ; % = 17	n = 171 ; % = 15
High blood pressure requiring medication No of events	n = 382 ; % = 46	n = 486 ; % = 43
Liver disease No of events	n = 17 ; % = 2	n = 22 ; % = 2
Stroke or other neurological problem No of events	n = 51 ; % = 6	n = 59 ; % = 5
Asthma, COPD or lung disease No of events	n = 72 ; % = 9	n = 174 ; % = 16
Antibiotics No of events	n = 61 ; % = 7	n = 77 ; % = 7
Duration of symptoms Days Median (IQR)	6 (4 to 9)	6 (4 to 9)
Received vaccination No of events	n = 111 ; % = 13	n = 108 ; % = 10
One dose No of events	n = 105 ; % = 13	n = 100 ; % = 9

Characteristic	Inhaled budesonide (N = 833)	Usual care (N = 1126)
Two doses No of events	n = 6 ; % = 1	n = 8 ; % = 1

Outcomes

Study timepoints

- 28 day

Primary outcomes

Outcome	Inhaled budesonide vs Usual care, 28 day, N2 = 787, N1 = 1069
Time to first reported recovery [Critical outcome] (days) first instance that a participant reports feeling recovered Hazard ratio/95% CI	1.21 (1.08 to 1.36)
Hospitalisation/ death [Critical outcome] Odds ratio/95% CI	0.75 (0.55 to 1.03)

Secondary outcomes

Outcome	28 day, Inhaled budesonide, N = 833	28 day, Usual care, N = 886
Sustained recovery [Important outcome] recovered by day 14 and remains recovered until day 28 No of events	n = 462 ; % = 59	n = 390 ; % = 49

Outcome	28 day, Inhaled budesonide, N = 833	28 day, Usual care, N = 886
Sustained recovery [Important outcome] recovered by day 14 and remains recovered until day 28 Sample size	n = 787 ; % = NA	n = 799 ; % = NA
Alleviation of all symptoms [Important outcome] all symptoms first reported as minor or none No of events	n = 630 ; % = 90	n = 666 ; % = 91
Alleviation of all symptoms [Important outcome] all symptoms first reported as minor or none Sample size	n = 701 ; % = NA	n = 732 ; % = NA
Initial reduction of severity of symptoms [Important outcome] No of events	n = 662 ; % = 84	n = 650 ; % = 82
Initial reduction of severity of symptoms [Important outcome] Sample size	n = 786 ; % = NA	n = 797 ; % = NA
Hospital assessment without admission [Critical outcome] No of events	n = 22 ; % = 3	n = 22 ; % = 3
Hospital assessment without admission [Critical outcome] Sample size	n = 786 ; % = NA	n = 797 ; % = NA
Oxygen administration [Important outcome] No of events	n = 50 ; % = 7	n = 73 ; % = 9
Oxygen administration [Important outcome]	n = 774 ; % = NA	n = 785 ; % = NA

Outcome	28 day, Inhaled budesonide, N = 833	28 day, Usual care, N = 886
Sample size		
Mechanical ventilation [Important outcome] No of events	n = 13 ; % = 2	n = 14 ; % = 2
Mechanical ventilation [Important outcome] Sample size	n = 776 ; % = NA	n = 784 ; % = NA
ICU admission [Important outcome] No of events	n = 10 ; % = 1	n = 21 ; % = 3
ICU admission [Important outcome] Sample size	n = 771 ; % = NA	n = 779 ; % = NA

Secondary outcomes (contrast)

Outcome	Inhaled budesonide vs Usual care, 28 day, N2 = NA, N1 = NA
Time to sustained recovery [Important outcome] (days) Sample size	n1 = 799 ; %1 = NA, n2 = 787 ; %2 = NA
Time to sustained recovery [Important outcome] (days) Hazard ratio/95% CI	1.39 (1.21 to 1.59)
Time to alleviations of all symptoms [Important outcome] (days) Sample size	n1 = 732 ; %1 = NA, n2 = 701 ; %2 = NA
Time to alleviations of all symptoms [Important outcome] (days)	1.07 (0.96 to 1.19)

Outcome	Inhaled budesonide vs Usual care, 28 day, N2 = NA, N1 = NA
Hazard ratio/95% CI	
Time to initial reduction of severity of symptoms [Important outcome] (days) Sample size	n1 = 797 ; %1 = NA, n2 = 786 ; %2 = NA
Time to initial reduction of severity of symptoms [Important outcome] (days) Hazard ratio/95% CI	1.19 (1.07 to 1.32)

Adverse events

Outcome	Inhaled budesonide, 28 day, N = 787	Usual care, 28 day, N = 1069
Serious adverse events [Critical outcome] No of events	n = 3 ; % = 1	n = 3 ; % = 1

Serious adverse events [Critical outcome] - Polarity - Lower values are better

Critical appraisal - Inhaled budesonide RoB

Primary outcomes - Time to first reported recovery

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Primary outcomes - Hospitalisation/death

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcome less likely to be influenced by knowledge of intervention allocation)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Secondary outcomes - Sustained recovery

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Secondary outcomes – Alleviation of all symptoms

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Secondary outcomes – Initial reduction of severity of symptoms

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Secondary outcomes – Hospital assessment without admission

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Secondary outcomes – Oxygen administration

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Secondary outcomes – Mechanical ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcome less likely to be influenced*

Section	Question	Answer
		by knowledge of intervention allocation)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Secondary outcomes – ICU admission

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Secondary outcomes(contrast) – Time to sustained recovery

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Secondary outcomes(contrast) – Time to alleviation of all symptoms

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Secondary outcomes(contrast) – Time to initial reduction of severity of symptoms

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Adverse events- Serious adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Ramakrishnan, 2021

Bibliographic Reference	Ramakrishnan, Sanjay; Nicolau, Dan V Jr; Langford, Beverly; Mahdi, Mahdi; Jeffers, Helen; Mwasuku, Christine; Krassowska, Karolina; Fox, Robin; Binnian, Ian; Glover, Victoria; Bright, Stephen; Butler, Christopher; Cane, Jennifer L; Halner, Andreas; Matthews, Philippa C; Donnelly, Louise E; Simpson, Jodie L; Baker, Jonathan R; Fadai, Nabil T; Peterson, Stefan; Bengtsson, Thomas; Barnes, Peter J; Russell, Richard E K; Bafadhel, Mona; Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial.; The Lancet. Respiratory medicine; 2021

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04416399
Study start date	16-Jul-2020
Study end date	09-Jul-2020
Aim of the study	To test if inhaled glucocorticoids would be an effective treatment for early COVID-19.
Country/geographical location	Oxfordshire, UK
Study setting	Primary care/Community
Population description	Adults aged older than 18 years with symptoms of COVID-19 (new onset cough and fever or anosmia, or both) within 7 days.

Inclusion criteria	
Exclusion criteria	Participants were excluded if they had recent use (within 7 days) of inhaled or systemic glucocorticoids or if they had a known allergy or contraindication to inhaled budesonide.
Intervention dosage (loading)	400 µg per actuation (two puffs to be taken twice per day; total dose 1600 µg)
Intervention dosage (maintenance)	
Intervention actual duration	Median duration was 7 days (range 4-10 days) Participants allocated to budesonide were asked to stop taking the inhaler when they felt they had recovered (self-reported symptom recovery) or if they hit the primary outcome; all participants ceased daily monitoring (including daily telephone calls) when symptoms had resolved (self-reported symptom recovery) or if the primary outcome was achieved.
Intervention route of administration	Inhaler
Comparator (where applicable)	Usual care was supportive therapy, with the National Health Service (NHS) advising patients with COVID-19 symptoms to take anti-pyretics for symptoms of fever (products containing paracetamol, or non-steroidal anti-inflammatories such as aspirin and ibuprofen) and honey for symptoms of cough.
Methods for population selection/allocation	Participants were randomly allocated to usual care or budesonide, stratified by participant age (≤40 years or >40 years), sex, and number of comorbidities (≤1 or ≥2). 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. The budesonide was open label.
Methods of data analysis	The primary outcome was analysed for both the per-protocol and intention-to-treat (ITT) population. The per-protocol population was defined as the population who received the study treatment and had at least 1 day of study observations. The ITT population was defined as all participants who were randomised to a study group

Attrition/loss to follow-up	Budesonide: 70/73 (96%) completed the trial • 1 person withdrew consent • 1 person needed urgent care before visit • 1 person discontinued intervention because it was too burdensome Usual: 69/73 (95%) completed the trial • 3 people withdrew consent • 1 person needed urgent care before visit
Source of funding	National Institute for Health Research Biomedical Research Centre and AstraZeneca.
Study limitations (Author)	• Open label study • The study was stopped early due to the impact of the national pandemic control measures, with a second national lockdown, and national prioritisation rules for clinical research trials in the UK, which prevented recruitment from outside the local region. • Study did not reach sample size but independent statistical simulations concluded that the final sample size and treatment effect had a 99% power to reject the null hypothesis
Study limitations (Reviewer)	Short term follow up (limited to 14 days).
Other details	Participants were seen at their homes at randomisation (day 0), day 7, and day 14 by a trained respiratory research nurse to obtain written informed consent, provide inhalers, and collect (self-performed) nasopharyngeal swabs for SARS-CoV-2 RT-PCR testing. Each participant received a paper symptom diary, calibrated pulse oximeter, and thermometer for daily home monitoring.

	All participants were contacted by telephone daily to record oxygen saturation and temperature, and to be assessed for any adverse events by the study team. At day 28, all study participants were seen in the trial centre and serum SARS-CoV-2 antibody testing was done. The trial was stopped early after independent statistical review concluded that study outcome would not change with further participant enrolment.

Study arms

Budesonide (N = 73)

Usual care (N = 73)

Characteristics

Arm-level characteristics

Characteristic	Budesonide (N = 73)	Usual care (N = 73)
Age Range	19 to 71	19 to 79
Age Sample size	n = 70 ; % = NA	n = 69 ; % = NA
Age Mean (SD)	44 (NR)	46 (NR)

Characteristic	Budesonide (N = 73)	Usual care (N = 73)
Gender Sample size	n = 70	n = 69
Female No of events	n = 39 ; % = 56	n = 41 ; % = 59
Male No of events	n = 31 ; % = 44	n = 28 ; % = 41
Ethnicity Sample size	n = 70	n = 69
White No of events	n = 65 ; % = 93	n = 64 ; % = 93
Non-white No of events	n = 5 ; % = 7	n = 28 ; % = 41
COVID-19 Disease severity Sample size	n = 70	n = 69
Mild Sample size	n = 70 ; % = 100	n = 69 ; % = 100
Comorbidities Sample size	n = 70	n = 60

Characteristic	Budesonide (N = 73)	Usual care (N = 73)
Cardiovascular disease No of events	n = 6 ; % = 9	n = 6 ; % = 9
Diabetes No of events	n = 3 ; % = 4	n = 4 ; % = 6
Past or current history of asthma No of events	n = 11 ; % = 16	n = 10 ; % = 14
Duration of symptoms (days) Sample size	n = 70	n = 69
Duration of symptoms (days) Median (IQR)	3 (2 to 5)	3 (2 to 4)
COVID-19 positive status No of events	n = 66 ; % = 94	n = 64 ; % = 94
COVID-19 positive status Sample size	n = 70	n = 69

Outcomes

Study timepoints

- 14 day

COVID-19-related urgent care visits

Outcome	Budesonide, 14 day, N = 73	Usual care, 14 day, N = 73
People who needed urgent care [Critical outcome] including emergency department assessment or hospitalisation No of events	n = 2 ; % = 3	n = 11 ; % = 15
People who needed urgent care [Critical outcome] including emergency department assessment or hospitalisation Sample size	n = 73 ; % = NA	n = 73 ; % = NA
Of which had positive COVID-19 status No of events	n = 1 ; % = 2	n = 8 ; % = 14
Of which had positive COVID-19 status Sample size	n = 66 ; % = NA	n = 65 ; % = NA

People who needed urgent care [Critical outcome] - Polarity - Lower values are better

Recovery

Outcome	Budesonide, 14 day, N = 70	Usual care, 14 day, N = 69
Self-reported clinical recovery [Important outcome] (days) p = 0.007 Median	7	8
Self-reported clinical recovery [Important outcome] (days) p = 0.007 95% CI	6 to 9	7 to 11

Outcome	Budesonide, 14 day, N = 70	Usual care, 14 day, N = 69
Of which had positive COVID-19 status p = 0.012 Median	7	8
Of which had positive COVID-19 status p = 0.012 95% CI	6 to 9	7 to 10
Time to recovery [Critical outcome] (days) Mean (SD)	8 (5)	12 (8)
Symptom resolution [Important outcome] No of events	n = 55 ; % = 82	n = 49 ; % = 72

Self-reported clinical recovery [Important outcome] - Polarity - Lower values are better
Time to recovery [Critical outcome] - Polarity - Lower values are better
Symptom resolution [Important outcome] - Polarity - Higher values are better
Adverse events

Outcome	Budesonide, 14 day, N = 70	Usual care, 14 day, N = 69
Adverse events [Important outcome] four had sore throat; one had dizziness No of events	n = 5 ; % = 7	n = NR ; % = NR

Adverse events [Important outcome] - Polarity - Lower values are better

Critical appraisal - Inhaled budesonide RoB

COVID-19 – related urgent care visits- People who needed urgent care

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Open label trial, However, participants were likely to have received an assessment prior to attending urgent care which may limit the bias)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

COVID-19 – related urgent care visits – People who needed urgent care of which had positive COVID-19 status

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Open label trial, However, participants were likely to have received an assessment prior to attending urgent care which may limit the bias)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Recovery- Self-reported clinical recovery

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Open label trial. Outcome is self-reported so may be influenced by knowledge of intervention allocation)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Recovery- Self-reported clinical recovery-Of which had positive COVID-19

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Open label trial. Outcome is self-reported so may be influenced by knowledge of intervention allocation)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Recovery - Symptom resolution

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Open label trial. Outcome is self-reported so may be influenced by knowledge of intervention allocation)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Open label trial. Outcome is self-reported so may be influenced by knowledge of intervention allocation)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E: Forest plots

Hospitalisation or death related to COVID-19 [SARS-CoV-2 positive only] (follow-up: 28 days)

No forest plot. Data as reported in study.

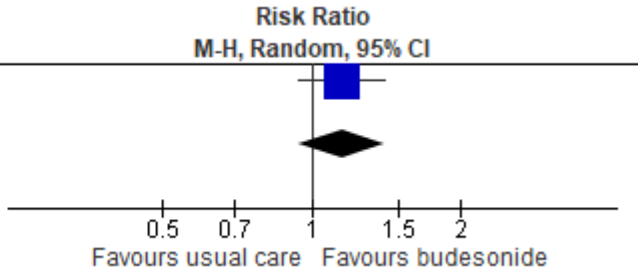
Time to alleviation of all symptoms [SARS-CoV-2 positive only]

No forest plot. Data as reported in study.

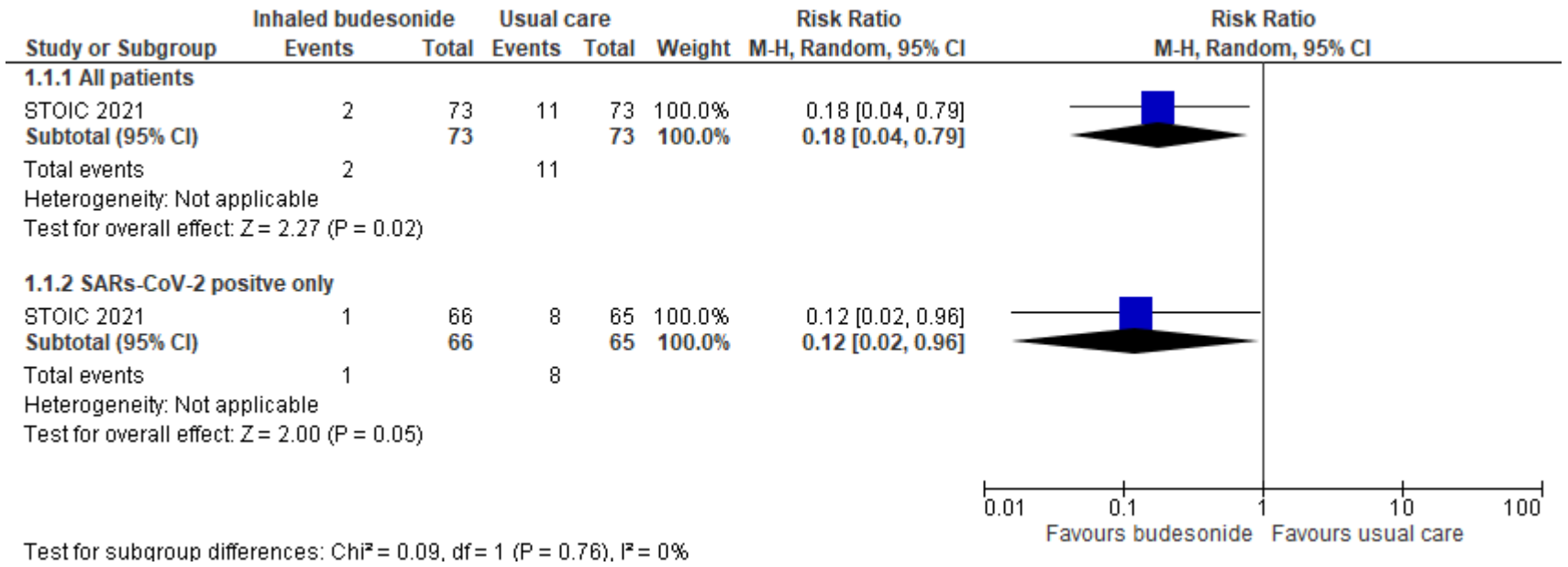
Alleviation of all of symptoms [SARS-CoV-2 positive only] (follow-up: 28 days)

	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
STOIC 2021	55	70	49	72	100.0%	1.15 [0.95, 1.41]
Total (95% CI)		**70**		**72**	**100.0%**	**1.15 [0.95, 1.41]**
Total events	55		49			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.41 (P = 0.16)



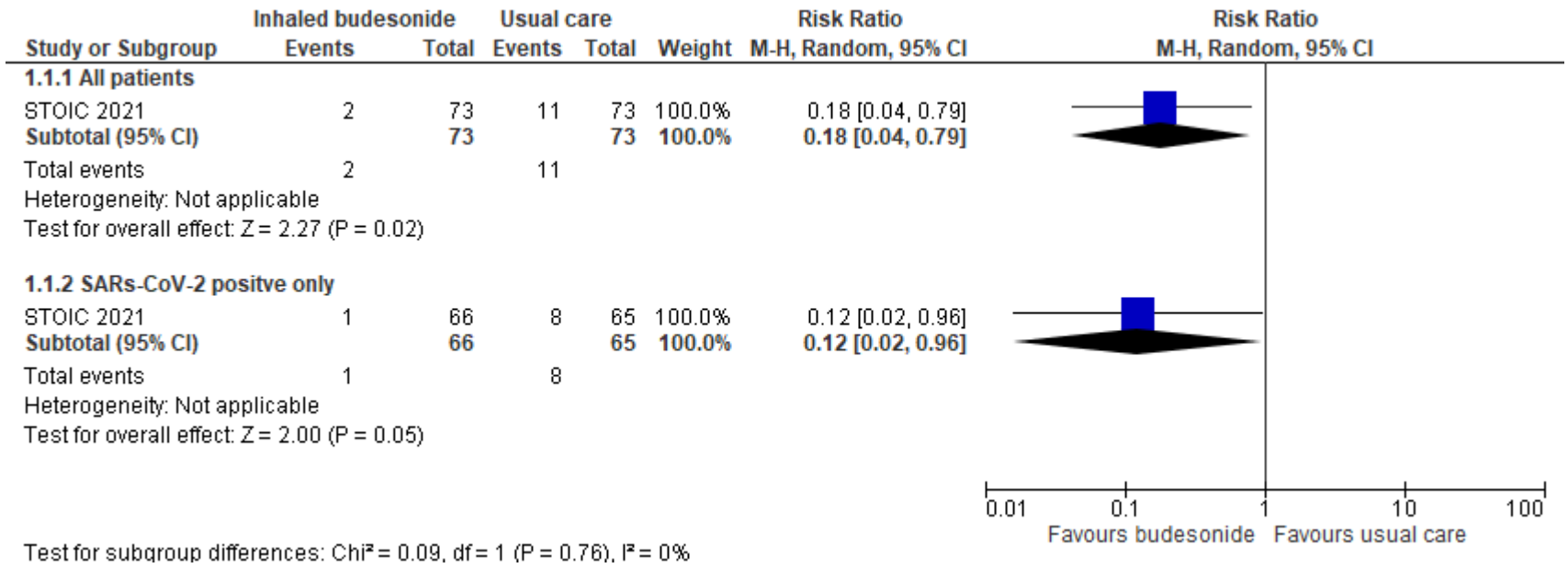
Symptom resolution (14 days)



Time to initial reduction of severity of symptoms [SARS-CoV-2 positive only]

No forest plot. Data as reported in study.

Initial reduction of severity of symptoms [SARS-CoV-2 positive only] (follow-up: 28 days)

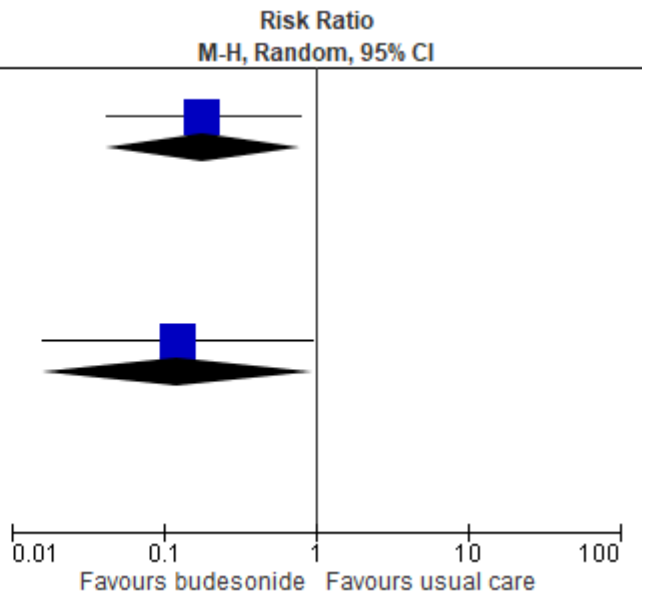


Time to sustained recovery [SARS-CoV-2 positive only]

No forest plot. Data as reported in study.

Sustained recovery [SARS-CoV-2 positive only] (follow-up: 28 days)

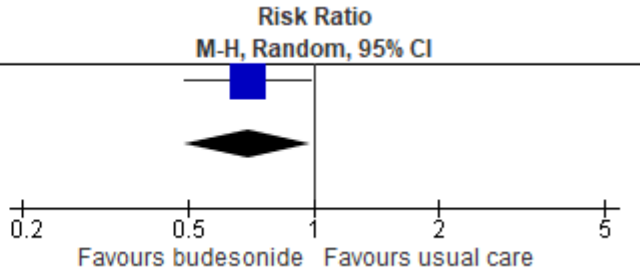
Study or Subgroup	Inhaled budesonide Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 All patients						
STOIC 2021	2	73	11	73	100.0%	0.18 [0.04, 0.79]
Subtotal (95% CI)		**73**		**73**	**100.0%**	**0.18 [0.04, 0.79]**
Total events	2		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.27 (P = 0.02)						
1.1.2 SARs-CoV-2 positve only						
STOIC 2021	1	66	8	65	100.0%	0.12 [0.02, 0.96]
Subtotal (95% CI)		**66**		**65**	**100.0%**	**0.12 [0.02, 0.96]**
Total events	1		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.00 (P = 0.05)						



Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² = 0%

Oxygen administration [SARS-CoV-2 positive only] (follow-up: 28 days)

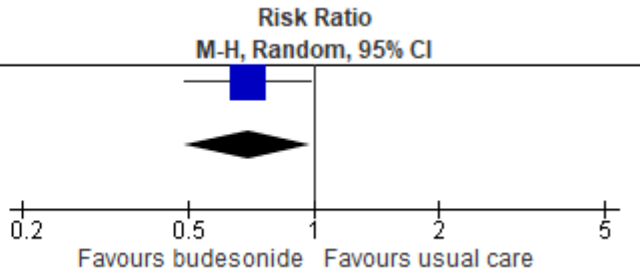
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
PRINCIPLE	50	774	73	785	100.0%	0.69 [0.49, 0.98]
Total (95% CI)		**774**		**785**	**100.0%**	**0.69 [0.49, 0.98]**
Total events	50		73			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.06 (P = 0.04)						



ICU admission [SARS-CoV-2 positive only] (follow-up: 28 days)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
PRINCIPLE	50	774	73	785	100.0%	0.69 [0.49, 0.98]
Total (95% CI)		**774**		**785**	**100.0%**	**0.69 [0.49, 0.98]**
Total events	50		73			

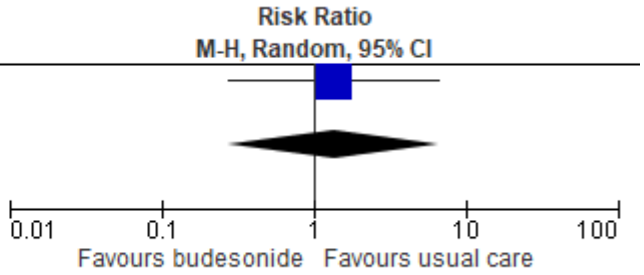
Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)



Hospitalisation or death related to COVID-19 [whole study population]

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
PRINCIPLE	3	787	3	1069	100.0%	1.36 [0.27, 6.71]
Total (95% CI)		**787**		**1069**	**100.0%**	**1.36 [0.27, 6.71]**
Total events	3		3			

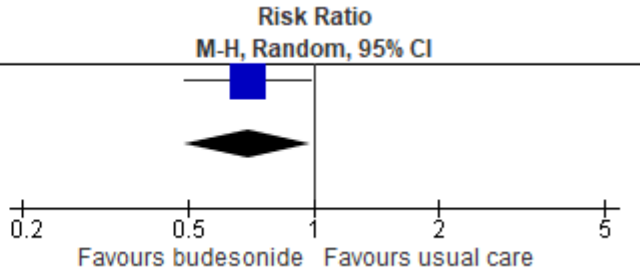
Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)



Mechanical ventilation [SARS-CoV-2 positive only]

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
PRINCIPLE	50	774	73	785	100.0%	0.69 [0.49, 0.98]
Total (95% CI)		**774**		**785**	**100.0%**	**0.69 [0.49, 0.98]**
Total events	50		73			

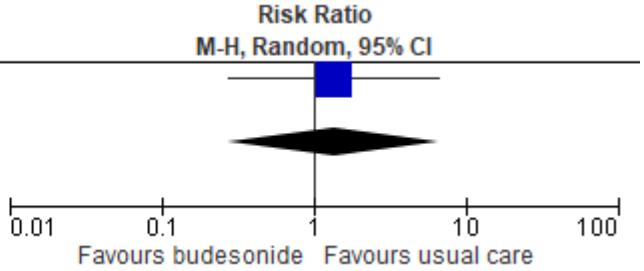
Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)



Serious adverse events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
PRINCIPLE	3	787	3	1069	100.0%	1.36 [0.27, 6.71]
Total (95% CI)		**787**		**1069**	**100.0%**	**1.36 [0.27, 6.71]**
Total events	3		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)



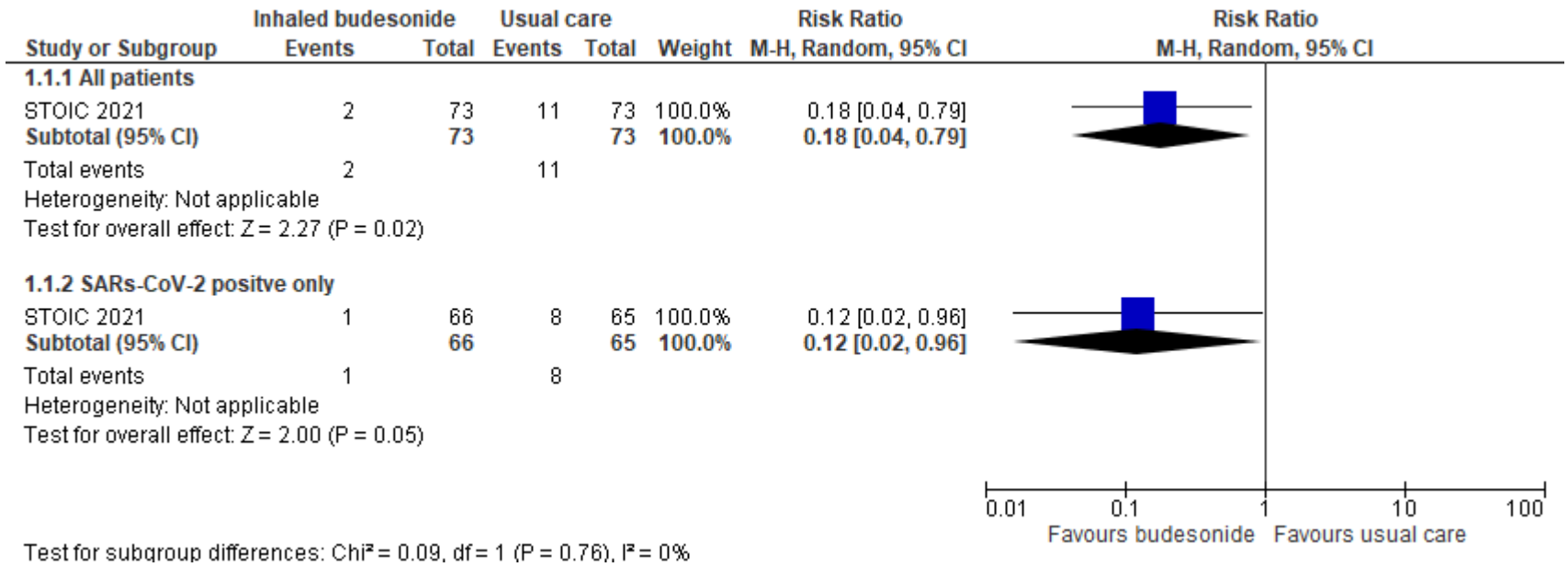
Time to first reported recovery [SARS-CoV-2 positive only]

No forest plot. Data as reported in study.

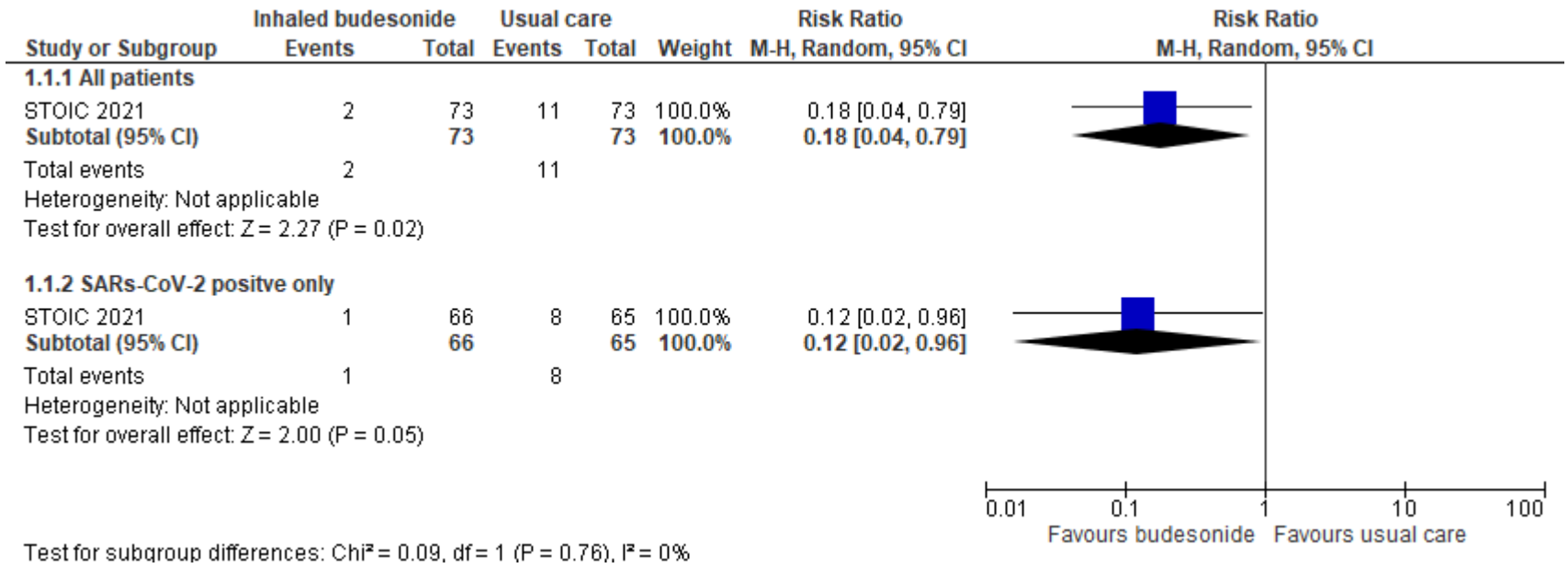
Time to first reported recovery [whole study population]

No forest plot. Data as reported in study.

COVID-19-related urgent care visits, including emergency department assessment or hospitalisation

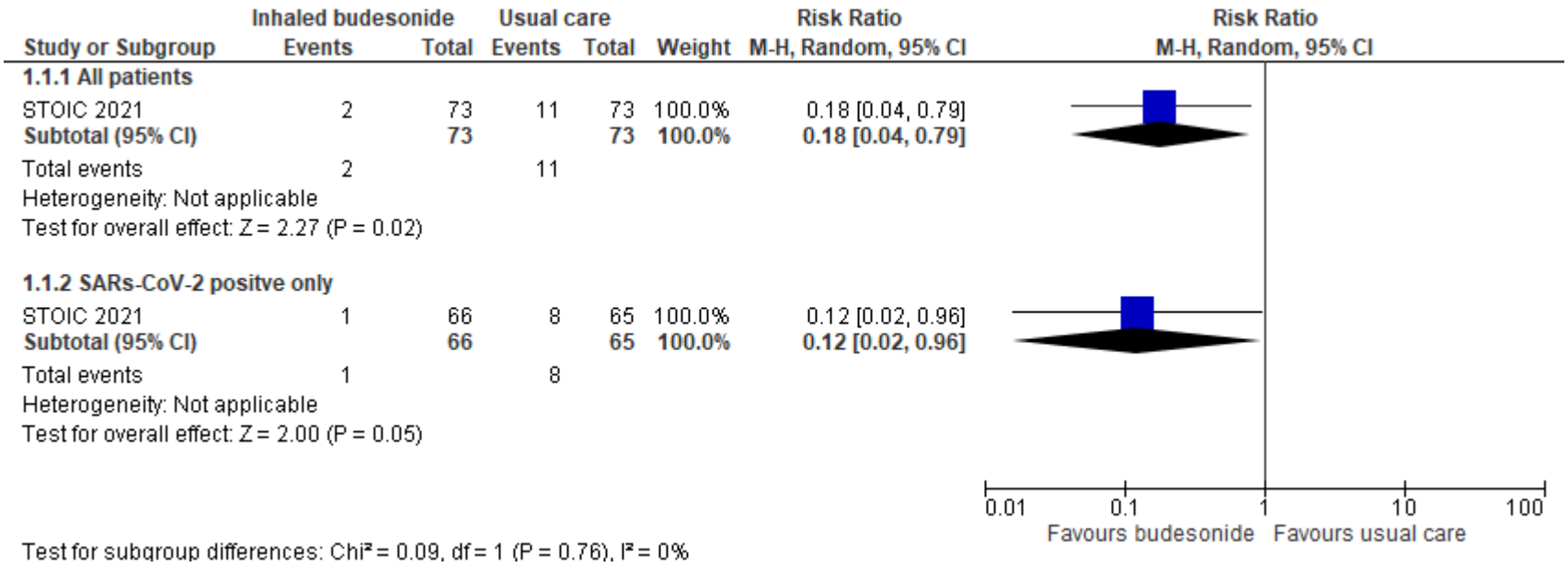


Hospital assessment without admission [SARS-CoV-2 positive only]



Time to recovery

No forest plot. Data as reported in study.


Inhaled budesonide
Usual care
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
1.1.1 All patients
STOIC 2021 2 73 11 73 100.0% 0.18 [0.04, 0.79]
Subtotal (95% CI) 73 73 100.0% 0.18 [0.04, 0.79]
Total events 2 11
Heterogeneity: Not applicable
Test for overall effect: Z = 2.27 (P = 0.02)
1.1.2 SARs-CoV-2 positve only
STOIC 2021 1 66 8 65 100.0% 0.12 [0.02, 0.96]
Subtotal (95% CI) 66 65 100.0% 0.12 [0.02, 0.96]
Total events 1 8
Heterogeneity: Not applicable
Test for overall effect: Z = 2.00 (P = 0.05)
0.01
0.1
1
10
100
Favours budesonide
Favours usual care
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² = 0%

Appendix F: GRADE tables

Inhaled budesonide compared to standard care for COVID-19

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard care	With inhaled budesonide		Risk with standard care	Risk difference with inhaled budesonide
Hospitalisation or death related to COVID-19 [SARS-CoV-2 positive only] (follow-up: 28 days)											
1856 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	NR	NR	**OR 0.75** (0.55 to 1.03)	NR	NR
Time to alleviation of all symptoms [SARS-CoV-2 positive only]											
14330 (1 RCT)	serious[b]	not serious	not serious	serious[a]	none	Low	NR	NR	**HR 1.07** (0.96 to 1.19)	NR	NR
Alleviation of all of symptoms [SARS-CoV-2 positive only] (follow-up: 28 days)											
1433 (1 RCT)	serious[b]	not serious	not serious	serious[a]	none	Low	666/732 (91.0%)	630/701 (89.9%)	**RR 0.99** (0.96 to 1.02)	910 per 1,000	**9 fewer per 1,000** (from 36 fewer to 18 more)
Symptom resolution (All patients) (follow-up: 14 days)											
142 (1 RCT)	serious[b]	not serious	not serious	serious[a]	none	Low	49/72 (68.1%)	55/70 (78.6%)	**RR 1.15** (0.95 to 1.41)	681 per 1,000	**102 more per 1,000** (from 34 fewer to 279 more)
Time to initial reduction of severity of symptoms [SARS-CoV-2 positive only]											

Certainty assessment							Summary of findings				
1583 (1 RCT)	serious[b]	not serious	not serious	not serious	none	Moderate	NR	NR	**HR 1.19** (1.07 to 1.32)	NR	NR
Initial reduction of severity of symptoms [SARS-CoV-2 positive only] (follow-up: 28 days)											
1583 (1 RCT)	serious[b]	not serious	not serious	serious[a]	none	Low	650/797 (81.6%)	662/786 (84.2%)	**RR 1.03** (0.99 to 1.08)	816 per 1,000	**24 more per 1,000** (from 8 fewer to 65 more)
Time to sustained recovery [SARS-CoV-2 positive only]											
1586 (1 RCT)	serious[b]	not serious	not serious	not serious	none	Moderate	NR	NR	**HR 1.39** (1.21 to 1.59)	NR	NR
Sustained recovery [SARS-CoV-2 positive only] (follow-up: 28 days)											
1586 (1 RCT)	serious[b]	not serious	not serious	not serious	none	Moderate	390/799 (48.8%)	462/787 (58.7%)	**RR 1.20** (1.10 to 1.32)	488 per 1,000	**98 more per 1,000** (from 49 more to 156 more)
Oxygen administration [SARS-CoV-2 positive only] (follow-up: 28 days)											
1559 (1 RCT)	not serious	not serious	not serious	not serious	none	High	73/785 (9.3%)	50/774 (6.5%)	**RR 0.69** (0.49 to 0.98)	93 per 1,000	**29 fewer per 1,000** (from 47 fewer to 2 fewer)
ICU admission [SARS-CoV-2 positive only] (follow-up: 28 days)											
1550 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	21/779 (2.7%)	10/771 (1.3%)	**RR 0.48** (0.23 to 1.01)	27 per 1,000	**14 fewer per 1,000** (from 21 fewer to 0 fewer)
Hospitalisation or death related to COVID-19 [whole study population] (follow-up: 28 days)											

Certainty assessment							Summary of findings				
2848 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	NR	NR	**OR 0.78** (0.57 to 1.04)	NR	NR
Mechanical ventilation [SARS-CoV-2 positive only] (follow-up: 28 days)											
1560 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	14/784 (1.8%)	13/776 (1.7%)	**RR 0.90** (0.44 to 1.98)	18 per 1,000	**2 fewer per 1,000** (from 10 fewer to 17 more)
Serious adverse events (follow-up: 28 days)											
1856 (1 RCT)	not serious	not serious	not serious	very serious[c]	none	Low	3/1069 (0.3%)	3/787 (0.4%)	**RR 1.36** (0.27 to 6.71)	3 per 1,000	**1 more per 1,000** (from 2 fewer to 16 more)
Time to first reported recovery [SARS-CoV-2 positive only]											
1856 (1 RCT)	serious[b]	not serious	not serious	not serious	none	Moderate	NR	NR	**HR 1.21** (1.08 to 1.36)	NR	NR
Time to first reported recovery [whole study population]											
2848 (1 RCT)	serious[b]	not serious	not serious	not serious	none	Moderate	NR	NR	**HR 1.18** (1.07 to 1.30)	NR	NR
COVID-19-related urgent care visits, including emergency department assessment or hospitalisation [whole study population] (follow-up: 14 days)											
146 (1 RCT)	not serious	not serious	serious[d]	not serious	none	Moderate	11/73 (15.1%)	2/73 (2.7%)	**RR 0.18** (0.04 to 0.79)	151 per 1,000	**124 fewer per 1,000** (from 145 fewer to 32 fewer)
COVID-19-related urgent care visits, including emergency department assessment or hospitalisation [SARs-CoV-2 positive only]											

Certainty assessment							Summary of findings				
131 (1 RCT)	not serious	not serious	serious[d]	not serious	none	Moderate	8/65 (12.3%)	1/66 (1.5%)	**RR 0.12** (0.02 to 0.96)	123 per 1,000	**108 fewer per 1,000** (from 121 fewer to 5 fewer)

Hospital assessment without admission [SARS-CoV-2 positive only] (follow-up: 28 days)

1583 (1 RCT)	serious[b]	not serious	not serious	serious[a]	none	Low	22/797 (2.8%)	22/786 (2.8%)	**RR 1.01** (0.57 to 1.82)	28 per 1,000	**0 fewer per 1,000** (from 12 fewer to 23 more)

Time to recovery

139 (1 RCT)	serious[b]	not serious	not serious	not serious	none	Moderate	NR	NR	-	NR	MD **4 Days lower** (6.22 lower to 1.78 lower)

CI: confidence interval; **HR:** hazard Ratio; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. 95% CI crosses the line of no effect
b. Open label study which may have influenced a subjective outcome.
c. 95% CI crosses the line of no effect and very few events
d. Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important)

Appendix G: Recommendations for research

Question	**What is the clinical and cost effectiveness of budesonide for treating COVID-19 in the community in adults, young people and children?**
Population	Adults, young people and children who have COVID-19 and are not in hospital Subgroups of particular interest: • People 18 to 49 years • Children and young people
Intervention(s)	Inhaled budesonide
Comparator(s)	Inhaled placebo (to accommodate blinding)
Outcomes	• All-cause mortality • Hospitalisation • Need for oxygen therapy (including thresholds for this decision) • Costs of treatment • Time to recovery • Health-related quality of life • Adverse events