National Institute for Health and Care Excellence

FINAL

Chronic obstructive pulmonary disease in over 16s: diagnosis and management

[J] Evidence reviews for the length of corticosteroid use during exacerbations

NICE guideline NG115

Evidence reviews

July 2019

Final

This evidence review was developed by the NICE Guideline Updates Team

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Corticosteroid use during exacerbations

Review question

Are shorter durations of ≤ 7 days of corticosteroid treatment effective at treating acute exacerbations in people with COPD compared to longer treatments of > 7 days?

Introduction

It is important to ensure that corticosteroid courses are not prescribed for longer than necessary due to the known adverse events associated with corticosteroid use, including fluid retention, pneumonia, hypertension, diabetes mellitus, adrenal suppression and osteoporosis. If there is an opportunity to shorten corticosteroid treatment without losing effectiveness this should be pursued in the interests of patient safety and quality of life. The NICE COPD guideline (NG115) currently recommends that patients with acute exacerbations of COPD should be treated with systemic corticosteroid treatment for 7 to 14 days. However, clinical practice has changed and courses of fewer than 7 days are now routinely used in the NHS. This review aims to investigate the evidence behind this change in practice and update the guideline accordingly. This review is based upon the 2018 Cochrane review "Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease" by Walters et al. (2018).

This review identified studies that fulfilled the conditions listed in Table 1, as specified in the protocol followed by the Cochrane Airways Group (Walters 2018). For full details of the review protocol, see appendix A.

PICO table

Table 1: PICO table for the duration of corticosteroid use during exacerbations

Population	Adults with an acute exacerbation of COPD. (The definition of an acute exacerbation could include any combination of an increase in breathlessness, sputum volume, sputum purulence, cough or wheeze.)
Interventions	Systemic corticosteroid (SCS) given for a period of seven or fewer days.
Comparator	Systemic corticosteroids given for longer than seven days.
Outcomes	• Treatment failure (for example, the need for additional treatment) • Relapse after treatment (e.g. treatment for new acute exacerbation, re-admission or hospitalisation for COPD) • Adverse drug effects • Mortality • Cardiac complications • Lung function (FEV1) • Length of hospital stay • Arterial blood gases • Breathlessness • Quality of life • Resource use and costs

	For continuous outcomes: early response was measured on or before day seven of treatment, and end of treatment response measurements were made at the time point equivalent to the end of the longer treatment period.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B.

Two of the subgroup analyses specified in the review protocol (inpatient versus outpatients and studies with people who had previously used corticosteroids versus corticosteroid naïve people) were not carried out for this review because the majority of included studies did not report data for the categories of interest in an accessible format. However, the majority of included studies could be divided into those administering corticosteroids orally or intravenously (IV) and so this subgroup analysis was conducted.

The GRADE tables only show the results of the subgroup analyses listed above if a difference between subgroups was detected based on a subgroup p value < 0.05. In all other cases, only the pooled results are presented.

The search strategies used in this review are detailed in appendix C.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Protocol deviation

A third subgroup analysis was undertaken to look for subgroup differences between the various lengths of the shorter corticosteroid course. In any outcomes where the subgroup I^2> 60% and there was data for the three short course durations the shortest course (3 days) was compared to the two longer courses (5 and 7 days) to determine whether a subgroup difference was detectable between these treatment durations (see the discussion for the rationale underlying this choice).

Clinical evidence

Included studies

A Cochrane review that matched that review protocol was identified ("Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease", Walters et al 2018). This review was judged to be of high quality according to the ROBIS systematic review quality checklist and was directly applicable. Consequently, it was used as a direct source of evidence for the review (see Appendix B for details of how published systematic reviews were incorporated).

The review is an update of an earlier Cochrane review. This update included the same 8 studies from the previous version of the Cochrane review as no new evidence was found.

The systematic search was updated by the Cochrane Airways Group on behalf of the Guideline Updates Team to identify any trials that were published after the final Cochrane review search. This search returned 166 results. Full details of the review protocol and literature search strategy can be found in appendix A and appendix C. After title and abstract screening all studies other than the 8 original includes and 1

new study were excluded. This single new study was excluded at full text screening due to the paper being a secondary publication of an included study that did not provide any additional relevant information.

As a result, the 8 studies included in this review are the 8 studies from the original Cochrane review. Of these studies, only 5 provided sufficient data on the outcomes of interest, trial methods and population to be included in the meta-analysis.

Two abstracts were included in the meta-analysis in the Cochrane review based on additional data obtained from the authors (Wood-Baker et al.1997 and Sirichana et al. 2008). For the other 3 abstracts identified by the Cochrane review, unpublished data was sought, but was insufficient for the studies to be included in the quantitative meta-analysis (Gomaa et al. 2008, Rahman et al. 2004, Salam et al. 1998).

The process of study identification is summarised in the PRISMA diagram in appendix D.

The references of individual included studies are listed in appendix J.

Excluded studies

Details of the study excluded at full-text, with reasons for exclusion, is given in appendix I.

Summary of clinical studies included in the evidence review

Only 5 of the studies included by the Cochrane review provided data that was appropriate to be meta-analysed. These studies reported on the following outcomes of interest:

- Treatment failure (4 studies)
- Relapse (4 studies)
- Adverse events (5 studies)
- Mortality (2 studies)
- Length of hospitalisation (3 studies)
- FEV1 (5 studies)
- PaO_2 (2 studies)
- $PaCO_2$ (1 study)
- Breathlessness (4 studies)
- Quality of life (1 study)

The ≤ 7 day corticosteroid period was recorded as 3 days (2 studies), 5 days (2 studies) or 7 days (1 study) and the > 7 day corticosteroid treatment was either 10 days (2 studies) or 14 days (3 studies).

Further characteristics are presented in Table 2.

Table 2: Summary of included study characteristics

Author	Days on treatment	Number of randomised people	Steroid used	Dose	Study location
Chen (2005)	7 days or 14 days	87	Oral prednisolone	30mg / day	China
Leuppi (2013)	5 days or 14 days	314	Day 1: IV methylprednisolone	40mg / day	Switzerland

			Day 2 - End: Oral prednisolone		
Sayiner (2001)	3 days or 10 days	36	IV methylprednisolone	Day 0-3: 0.5 mg/kg 6-hourly Day 4-6: 0.5 mg/kg 12-hourly Day 6-10: 0.5 mg/kg /day	Turkey
Sirichana (2008)	5 days or 10 days	48	Prednisolone (unspecified delivery method)	30mg / day	Thailand
Wood-Baker (1997)	3 days or 14 days	38	Oral prednisolone	Less than 7 days group: 2.5 mg/kg / day for 3 days followed by 11 days placebo Greater than 7 days group: Day 0-7 0.6 mg/kg Day 7-14 0.3 mg/kg	Australia

Please refer to the evidence tables in the Cochrane review for more details about the included studies.

Quality assessment of clinical studies included in the evidence review

The quality assessments for the 5 studies included in the meta-analysis was based on the judgments of the Cochrane review authors who used the Cochrane Risk of Bias tool. This is the same method as used by NICE for risk of bias assessment and so the Guidelines Updates Team used this information to generate an overall study risk of bias. This is shown in appendix E. For full GRADE tables please see appendix G.

Economic evidence

A systematic search was carried out to cover this review question. The search returned 267 records, all of which were excluded on title and abstract.

Evidence statements

The format of the evidence statements is explained in appendix B. Unless stated, the results presented in the evidence statements are pooled results and are not separated by method of administration. Sub-group analysis results are only presented where there were significant differences between subgroups.

Shorter durations of ≤ 7 days of corticosteroid treatment vs longer treatments of > 7 days

Moderate to high quality evidence from up to 4 RCTs with up to 404 people found no meaningful difference in early or 15 day breathlessness symptoms, 6 day quality of life or 30 day quality of life in people with a COPD exacerbation offered corticosteroid treatment for ≤ 7 days compared to people with a COPD exacerbation offered corticosteroid treatment > 7 days.

Low to moderate quality evidence from up to 5 RCTs with up to 503 people could not differentiate treatment failure, relapse, time to re-exacerbation, adverse event levels, mortality, length of hospitalisation, FEV1, PaO_2, or $PaCO_2$ in people with a COPD exacerbation offered corticosteroid treatment for ≤ 7 days compared to people with a COPD exacerbation offered corticosteroid treatment for > 7 days.

Subgroup analyses

No subgroup differences were identified between studies with people on an oral corticosteroid course studies with people receiving corticosteroids by IV, studies with people receiving corticosteroids by IV followed by an oral corticosteroid course, or studies with people receiving corticosteroids by an unknown mechanism of delivery, apart from FEV1 at the end of treatment.

- Moderate quality evidence from 1 study with 34 people who received corticosteroids by IV showed an improvement in FEV1 at 12 months in people with a COPD exacerbation offered corticosteroid treatment for > 7 days compared to people with a COPD exacerbation offered corticosteroid treatment for ≤ 7 days
- Very low to moderate quality evidence in up to 3 studies with up to 110 people who were on an oral corticosteroid course or who received corticosteroids by an unknown mechanism of delivery could not differentiate FEV1 in people with a COPD exacerbation offered corticosteroid treatment for ≤ 7 days compared to people with a COPD exacerbation offered corticosteroid treatment for > 7 days.

No subgroup differences were identified between studies with people on a 3 day, 5 day or 7 day course of corticosteroids compared to a course of >7 days.

Subgroup differences were identified for breathlessness at 15 days between studies with differing lengths of shorter corticosteroid course (3 days against 5 or 7 days) compared to people a longer course of >7 days.

- Moderate quality evidence in up to 2 studies with up to 52 people who had a shorter corticosteroid course of 3 days showed an increase in breathlessness at 15 days people with a COPD exacerbation compared to people with a COPD exacerbation offered corticosteroid treatment for > 7 days, but the point estimate was less than the defined clinically meaningful difference.
- High quality evidence in up to 2 studies with up to 352 people who had a shorter corticosteroid course of 5 or 7 days showed no meaningful difference in breathlessness at 15 days in people with a COPD exacerbation days compared to people with a COPD exacerbation offered corticosteroid treatment for > 7 days.

Sensitivity analyses removing studies at high risk of bias

Sensitivity analyses were carried out to remove studies at high risk of bias. These analyses did not lead to any changes in the interpretation of the evidence.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that since the oral corticosteroid use under review was taking place during an exacerbation, the key outcomes for a person with COPD under these circumstances were related to length of hospitalisation, breathlessness, time to re-exacerbation, mortality and quality of life. In addition, treatment failure and relapse were measures of the effectiveness of the treatment and it was important to examine the numbers of people experiencing adverse events associated with oral corticosteroid use to help determine the benefits of a shorter course of medication. Outcome measures such as FEV1, PaO_2 and $PaCO_2$ could be useful indicators of physiological improvement for the person taking the corticosteroid courses, but would not be sufficiently important in the absence of improvements in the aforementioned outcomes to make decisions regarding oral corticosteroid use.

The quality of the evidence

The evidence for the outcomes in this review ranged from very low to high quality. All studies were judged to be directly applicable, and one was judged to be at high risk of bias due to participants, investigators and outcome assessors not being blinded (Sirichana et al. 2008). All other studies were judged to be at low risk of bias. However, the sensitivity analysis removing Sirichana 2008 showed no difference in results for any of the outcomes.

Whilst two of the studies in the meta-analysis were published abstracts (Wood-baker 1997 and Sirichana 2008), the authors of the Cochrane review that this review is based upon obtained extra unpublished data from the authors, leading to a more reliable data source than the published abstract alone. However, neither study has been published as a full paper or been through peer review.

With regards to the study population, the committee noted that many of the studies were from lower income countries that may have demographic characteristics that are less relevant to UK practice. The committee also noted that all of the evidence came from a hospital setting (if a setting was recorded), and expressed concerns about the lack of evidence regarding oral corticosteroid use in outpatients, for example in community settings. However, they agreed that the findings remained sufficiently relevant for the UK population in general and decided against downgrading the evidence for indirectness. Further concerns around the quality of the evidence included the age of the data (the studies were carried out between 1997 and 2013), there was a lack of information about % of males or females in some trials and the doses of oral corticosteroids used. The committee discussed the high percentage of males in these studies, particularly in Sayiner 2001, which may be due to the difference in smoking habits between males and females in the countries the studies took place in. The committee also stated that the prednisolone dose of 2.5mg/kg per day used in Wood-baker (1997) is much higher than UK doses.

Data was only available for one of the subgroups outlined in the review protocol, regarding which mechanism of corticosteroid delivery occurred in each trial. The only subgroup difference was observed in the FEV1 end of treatment results, where the IV group showed an improvement in patients given corticosteroid for > 7 days. The committee agreed this result was not important with regards to recommendations,

due to the low patient number in this study and the low relative importance of FEV1 compared to the other outcomes.

Benefits and harms

The aim of this review was to determine whether there was any detectable difference in outcomes between a ≤ 7 day course of corticosteroids and > 7 day course of corticosteroids. However, the committee noted that the use of even shorter courses of corticosteroids is already widespread in clinical practice.

For most outcomes, the evidence could not differentiate between longer and shorter courses of corticosteroids. In particular, breathlessness, which was highlighted as one of the important outcomes, and quality of life showed no meaningful difference between the longer and shorter corticosteroid courses. However, the committee noted that the absence of a meaningful difference did not necessarily mean that the treatment durations were equivalent, particularly as the small sample size of some of the trials might have prevented any differences from being detected. Despite this, based on their clinical experience, and supported by the results of the larger trials (Chen, 2005, and Leuppi, 2013), the committee agreed that it was likely that the effects of courses of ≤ 7 days of steroids were equivalent to courses of > 7 days.

For breathlessness (early and at 15 days), the quality of evidence was high to moderate from 4 studies and 404 patients, with the 95% confidence intervals (CIs) well within the minimal clinically important differences (MIDs), suggesting that there is an absence of clinically meaningful difference for this outcome. For quality of life, the evidence quality was high in one study with up to 290 patients in the intention to treat analysis population. The 95% CIs again were well within the MIDs. It is worth noting that these analyses had MIDs taken from the clinical literature as opposed to using the line of no effect or default values (0.8 and 1.25 for RRs) as a measure of imprecision.

The committee discussed whether they could make a recommendation for a specific short duration (3, 5 or 7 days). They examined the results of subgroup analyses that stratified the results for each outcome by the different short course durations. No significant subgroup differences ($P<0.05$) were detected in these analyses, however, the p value was relatively close to 0.05 ($P<0.08$) for breathlessness at 15 days when comparing the 3,5 and 7 day subgroups and the I^2 was large at 61.1%, indicating high levels of heterogeneity. When the shortest course of 3 days was compared to the pooled subgroup of 5 and 7 days, a subgroup difference was detected ($P<0.03$) between these groups implying that the 3-day course was different to the 5/7 day courses in relation to effects on breathlessness at 15 days, with breathless being worse in the 3 day group compared to the 5/7 day group. No other evidence suggested that the 3 day course was worse than the 5 or 7 day course durations. When the committee took into account the MID for the Borg breathlessness scale they noted that after 15 days, the 5/7 day group showed no meaningful difference in breathlessness compared to people offered >7 days treatment. In contrast, people offered 3 days of treatment showed a worsening of breathlessness compared to people offered >7 days treatment, but the point estimate was less than the defined clinically meaningful difference. Taking these factors into account, the committee agreed to recommend a course duration of 5 days, but because there was the possibility that breathlessness could be worse in people treated with oral corticosteroids for only 3 days compared to longer treatment durations, they agreed not to reduce the duration any further.

The committee noted that there was no evidence of benefit from taking corticosteroids for more than 7 days and emphasised the importance of stopping

treatment at this point rather than weaning the person off prednisolone as may sometimes happen in current practice.

The committee stated that if there is no positive effect associated with a longer corticosteroid course the shorter course should be recommended to reduce the risk of corticosteroid side effects, including fluid retention, pneumonia, hypertension, diabetes mellitus, adrenal suppression and osteoporosis. This also reduces the risk of clinicians not just stopping oral corticosteroids but weaning people off slowly instead, which then further increases oral corticosteroid exposure without benefit. The committee noted that while the evidence could not differentiate between the two courses for adverse events, long term oral corticosteroid use over time as a result of repeated courses would likely increase the risk of adverse events. Thus, a shorter course would likely be beneficial for the individual over time as the total amount of oral corticosteroids prescribed and taken annually would be reduced.

Cost effectiveness and resource use

The committee discussed the cost effectiveness of prescribing ≤ 7 days versus > 7 days of corticosteroid treatment for acute exacerbations. They determined that, given the lack of evidence of any additional clinical benefit for treatment past 7 days, the more conservative choice of a shorter treatment duration is likely to be cost effective by reducing the indirect costs of corticosteroids (i.e. from adverse effects). Furthermore, the committee highlighted that outcomes included in the clinical review do not capture the potential longer-term consequences of corticosteroid use, such as osteoporosis. Therefore, it is reasonable to expect that treatment for ≤ 7 days is both less costly overall, and produces equivalent or better health outcomes than treatment for > 7 days.

The committee discussed the potential resource impact of their recommendation, and determined that it may produce a cost saving, due to reduced use of corticosteroids. However, the overall impact is likely to be small, given the low cost of oral corticosteroids, and given that prescribing corticosteroids for ≤ 7 days is current practice for many clinicians.

Other factors the committee took into account

The committee expressed an interest in examining the doses of oral corticosteroids used in addition to the duration of the courses, but this was outside of the scope of this review question and update. Instead, they retained the dose from the recommendation in the 2018 guideline, which was based on a 2004 review that examined the evidence for oral corticosteroid use in detail.

The committee also discussed the importance of clearly informing people whether they are being prescribed higher strength tablets to make the dose of 30mg or multiple tablets of a lower dose (commonly 6 tablets of 5mg). This may help to reduce the risk of an accidental overdose, particularly if a person moves between different care settings where the format of the dose may change. However, the committee felt that this issue was generally applicable to situations other than corticosteroid use in people with COPD and therefore did not require a specific recommendation to be made.

The committee noted that standard oral corticosteroid prescribing is of plain oral prednisolone tablets. They noted that soluble and enteric coated corticosteroid tablets exist and are more expensive than other forms of tablets. They were unable to recommend any conditions for their use because this area was not within the

scope of this review question and they did not examine any evidence regarding the cost and clinical effectiveness of different tablets.

The committee also noted that the current recommendation for oral corticosteroid courses of 5 days duration to treat an exacerbation was in line with the duration of antibiotic treatment. This makes it easier for patients when both medications are included in the rescue packs that form part of a self-management action plan or when oral corticosteroid and antibiotic courses are prescribed directly to treat exacerbations. Matching the course durations may make it easier for people to manage their medications and thus increase adherence.

The committee discussed whether people with COPD and overlapping asthma would require different or extended treatment for a COPD exacerbation compared to people with COPD only. The Cochrane review, that was the source of information for this update, included people who had COPD only, without comorbidities. This meant that the population of people with COPD and overlapping asthma was not captured as part of this review. The committee decided that there was no evidence in the review that could justify giving people with COPD and overlapping asthma an extended course of treatment, but based on their clinical experience there would not be any difference in treatment of a COPD exacerbation for people with COPD and overlapping asthma compared to people with COPD only. The committee noted that if a person with COPD and asthma has an asthma exacerbation then they should be treated for that exacerbation according to NICE asthma guidelines.

Appendices

Appendix A – Review protocols

Review protocol for the duration of corticosteroid use during exacerbations

Field (based on PRISMA-P)	Content
Review question	Are shorter durations of ≤ 7 days of corticosteroid treatment effective at treating acute exacerbations in people with COPD compared to longer treatments of > 7 days?
Type of review question	Intervention
Objective of the review	To determine whether shorter durations (≤ 7 days) of corticosteroid treatment can be used to treat exacerbations in people with COPD instead of the longer treatments (>7 days) that are currently recommended by the NICE COPD guideline CG101 (2010).
Eligibility criteria – population	Inclusion criteria from Cochrane Review: Adults with an acute exacerbation of COPD. (The definition of an acute exacerbation could include any combination of an increase in breathlessness, sputum volume, sputum purulence, cough or wheeze.)
Eligibility criteria – interventions	Systemic corticosteroid (SCS) given for a period of seven or fewer days.
Eligibility criteria – comparators	Systemic corticosteroids given for longer than seven days.
Outcomes	• Treatment failure (for example, the need for additional treatment) • Relapse after treatment (e.g. treatment for new acute exacerbation, re-admission or hospitalisation for COPD) • Adverse drug effects • Mortality • Cardiac complications • Lung function (FEV1)

	• Length of hospital stay • Arterial blood gases • Breathlessness • Quality of life • Resource use and costs For continuous outcomes: early response was measured on or before day seven of treatment, and end of treatment response measurements were made at the time point equivalent to the end of the longer treatment period.
Eligibility criteria – study design	RCTs
Other exclusion criteria	• Studies that included patients with asthma and other lung diseases (e.g. interstitial lung disease, bronchiectasis), unless separate data on participants with COPD alone were available. • Studies in which participants received assisted ventilation (invasive or non-invasive).
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups: • Inpatient versus outpatient • Studies that included participants previously treated with corticosteroids (inhaled and systemic) • Oral versus IV administration
Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.

	This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See Appendix B
Information sources – databases and dates	See Appendix C
Identify if an update	Partial update of 2004 COPD guideline question: Are oral steroids useful / effective in the treatment of patients with an exacerbation of COPD? (2004)
Author contacts	Guideline update
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables).
Methods for assessing bias at outcome/study level	See Appendix B
Criteria for quantitative synthesis	See Appendix B
Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
Meta-bias assessment – publication bias, selective reporting bias	See Appendix B

Confidence in cumulative evidence	See Appendix B
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Andrew Molyneux in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
PROSPERO registration number	N/A

Appendix B – Methods

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 3. When systematic reviews were used as a source of primary data, and unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE/CERQual tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 3: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately. For continuous outcomes analysed as standardised mean differences, where only baseline and final time point values were available, change from baseline standard deviations were estimated, assuming a correlation coefficient of 0.5.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials).

Fixed- and random-effects models (der Simonian and Laird) were used, with the choice of model based on the degree of heterogeneity for the results of each outcome. Fixed-effects models were the preferred choice, but in situations where the assumptions of a shared mean for fixed-effects model were clearly not met, random-effects results were presented. Random-effects models were selected for analysis if significant statistical heterogeneity was identified in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager V5.3, with the exception of incidence rate ratio analyses which were carried out in R version 3.3.4.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

MIDs found through this process and used to assess imprecision in the guideline are given in Table 4. For other continuous outcomes not specified in the table below, no MID was defined and the line of no effect was used instead.

Table 4: Identified MIDs

Outcome	MID	Source
Borg dyspnoea (breathlessness) score	2 units (-2, +2)	Ries AL. Minimally clinically important difference for the UCSD shortness of breath questionnaire, Borg Scale, and Visual Analog Scale. J COPD 2005; 2: 105–110.
Change in FEV1	0.1 L (-0.1, +0.1)	Cazzola M, MacNee W, Martinez M et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008; 31: 416–468.
Acute bronchitis health-related quality of life interview	0.5 units (-0.5, +0.5)	Evans AT, Husain S, Durairaj L, Sadowski LS, et al. Azithromycin for acute bronchitis: A randomised, double-blind controlled trial. The Lancet 2002, 359(9318), 1648-54.

The committee specified that any difference in mortality would be clinically meaningful, and therefore the line of no effect was used as an MID. For relative risks where no other MID was available, the GRADE default MID interval for dichotomous outcomes of 0.8 to 1.25 was used. Incidence rate ratios were treated in the same way as relative risks, with a default MID interval of 0.8 and 1.25 used for analysis.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 5.

Table 5: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies

GRADE criteria	Reasons for downgrading quality
	(heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

Evidence statements for pairwise intervention data are classified in to one of four categories:

For outcomes with a defined MID, evidence statements were divided into 4 groups as follows:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is

most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.

- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

Appendix C – Literature search strategies

Clinical literature search

The clinical literature search was undertaken by Cochrane, and outlined in full in the 2018 review. The approach comprises a search to populate the Cochrane Airways Trial Register, and additional searches of MEDLINE, CENTRAL and Embase. The MEDLINE search for this review is presented below.

1 COPD[MeSH Terms]

2 "adrenal cortex hormone*"

3 steroid

4 steroids

5 glucocorticoid*

6 corticoid*

7 corticosteroid*

8 beclomethasone

9 betamethasone

10 fluticasone

11 cortisone

12 dexamethasone

13 hydrocortisone

14 prednisolone

15 prednisone

16 methylprednisolone

17 methylprednisone

18 triamcinolone

#19 (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)

20 randomised controlled trial [pt]

21 controlled clinical trial [pt]

22 randomised [tiab]

23 placebo [tiab]

24 clinical trials as topic [mesh: noexp]

25 randomly [tiab]

26 trial [ti]

27 (#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)

28 (animals [mh] NOT humans [mh])

29 (#27 NOT #28)

30 ("2012/01/01"[Date - Publication] : "3000"[Date - Publication])

31 (#1 AND #19 AND #29 AND #30)

Health economics literature search

Economic evaluations and quality of life data

Sources searched:

- NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
- Health Technology Assessment (HTA Database)
- EconLit (Ovid)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Search filters to retrieve economic evaluations and quality of life papers were appended to population terms in MEDLINE, MEDLINE IN-Process and Embase to identify relevant evidence and can be seen below. Searches were carried out on 4th and 8th October 2018.

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. .

1 lung diseases, obstructive/
2 exp pulmonary disease, chronic obstructive/
3 (copd or coad or cobd or aecb).tw.
4 emphysema*.tw.
5 (chronic* adj4 bronch*).tw.
6 (chronic* adj3 (airflow* or airway* or bronch* or lung* or respirat* or pulmonary) adj3 obstruct*).tw.
7 (pulmonum adj4 (volumen or pneumatosis)).tw.
8 pneumonectasia.tw.
9 *Dyspnea/
10 (chronic* adj3 (breath* or respirat*) adj3 (difficult* or labor* or labour* or problem* or short*)).tw.
11 (chronic* adj3 (dyspnea* or dyspnoea* or dyspneic or breathless*)).tw.
12 or/1-11
13 exp Adrenal Cortex Hormones/
14 "adrenal cortex hormone*".tw.
15 Steroids/
16 steroid*.tw.
17 glucocorticoid*.tw.
18 cortico*.tw.
19 (beclomethasone* or beclometasone*).tw.
20 betamethasone*.tw.

21 exp Fluticasone/
22 fluticasone*.tw.
23 Cortisone/
24 cortisone*.tw.
25 deflazacort*.tw.
26 calcort*.tw.
27 dexamethasone*.tw.
28 glensoludex*.tw.
29 dexsol*.tw.
30 martapan*.tw.
31 exp Hydrocortisone/
32 hydrocortisone*.tw.
33 prednisolone*.tw.
34 pevanti*.tw.
35 prednisone*.tw.
36 deltacortril*.tw.
37 dilacort*.tw.
38 methylprednis*.tw.
39 medrone*.tw.
40 triamcinolone*.tw.
41 Pregnenediones/
42 (pregnenedi*).tw.
43 sterapred*.tw.
44 or/13-43
45 (short* adj3 (duration* or course or treatment* or therapy*)).tw.
46 (("7" or "6" or "5" or "4" or "3" or "2" or "1" or seven or six or five or four of three or two or one) adj3 day*).tw.
47 ("1 week" or "one week").tw.
48 or/45-47
49 44 and 48
50 12 and 49

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in MEDLINE in Process and Embase databases.

<u>Economic evaluations</u>
1. Economics/
2. exp "Costs and Cost Analysis"/
3. Economics, Dental/
4. exp Economics, Hospital/
5. exp Economics, Medical/
6. Economics, Nursing/
7. Economics, Pharmaceutical/
8. Budgets/
9. exp Models, Economic/
10. Markov Chains/
11. Monte Carlo Method/
12. Decision Trees/
13. econom$.tw.
14. cba.tw.
15. cea.tw.
16. cua.tw.
17. markov$.tw.

18. (monte adj carlo).tw.
19. (decision adj3 (tree$ or analys$)).tw.
20. (cost or costs or costing$ or costly or costed).tw.
21. (price$ or pricing$).tw.
22. budget$.tw.
23. expenditure$.tw.
24. (value adj3 (money or monetary)).tw.
25. (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26. or/1-25

Quality of Life
1. "Quality of Life"/
2. quality of life.tw.
3. "Value of Life"/
4. Quality-Adjusted Life Years/
5. quality adjusted life.tw.
6. (qaly$ or qald$ or qale$ or qtime$).tw.
7. disability adjusted life.tw.
8. daly$.tw.
9. Health Status Indicators/
10. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15. (euroqol or euro qol or eq5d or eq 5d).tw.
16. (qol or hql or hqol or hrqol).tw.
17. (hye or hyes).tw.
18. health$ year$ equivalent$.tw.
19. utilit$.tw.
20. (hui or hui1 or hui2 or hui3).tw.
21. disutili$.tw.
22. rosser.tw.
23. quality of wellbeing.tw.
24. quality of well-being.tw.
25. qwb.tw.
26. willingness to pay.tw.
27. standard gamble$.tw.
28. time trade off.tw.
29. time tradeoff.tw.
30. tto.tw.
31. or/1-30

Appendix D – Clinical evidence study selection

Figure 1: Study flow diagram – taken from the published Cochrane review (Walters 2018)

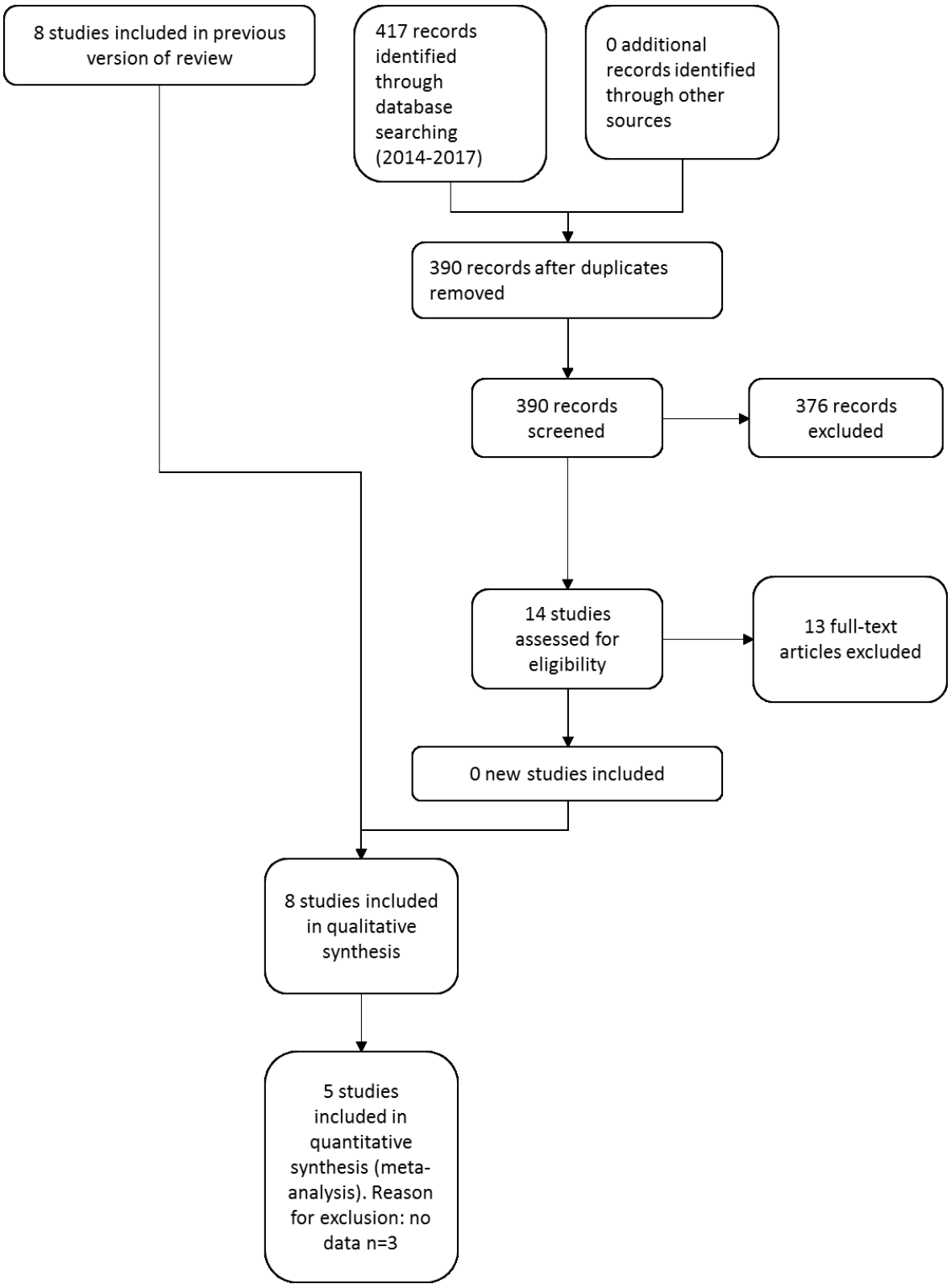
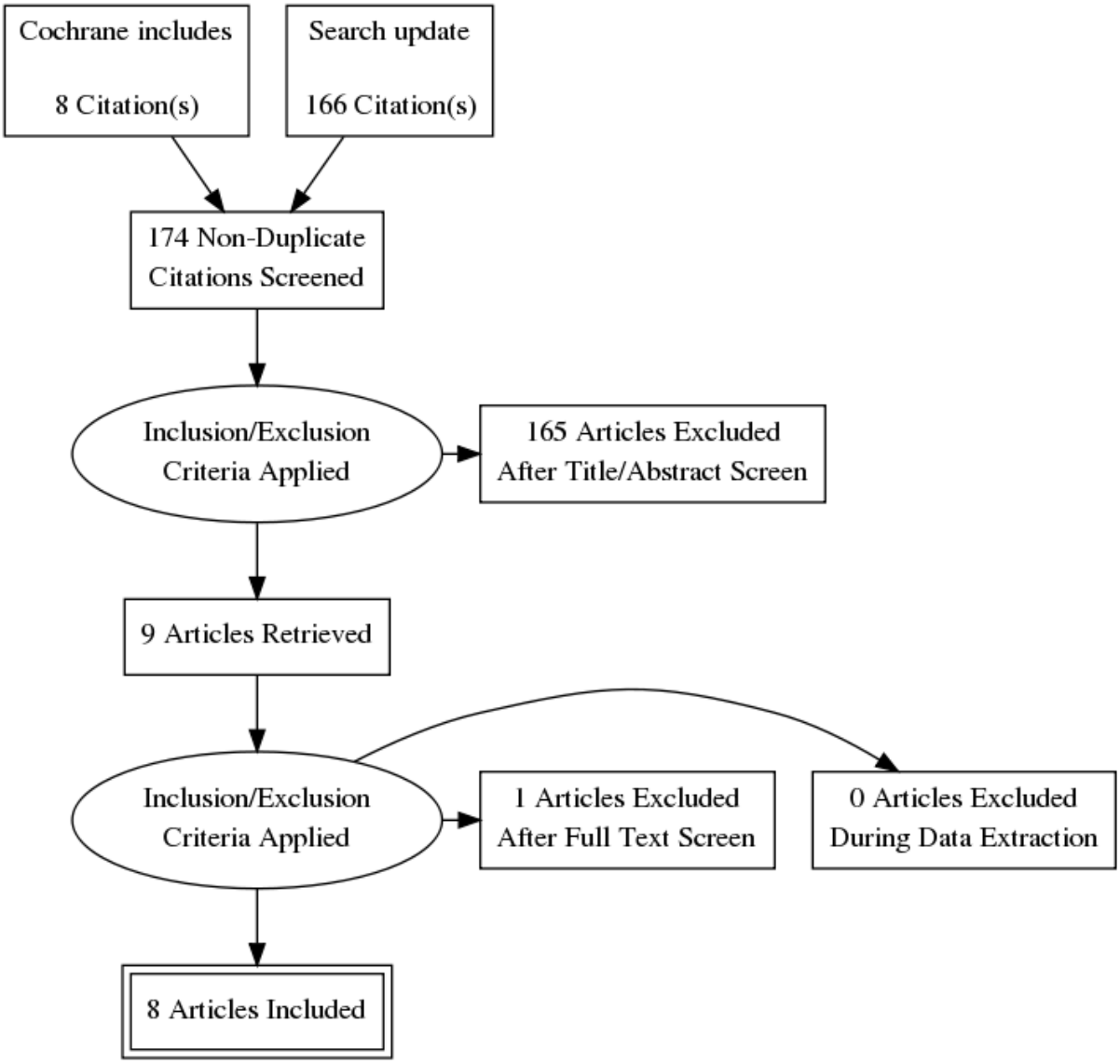


Figure 2: Study flow diagram – Cochrane update search for guideline updates team



Appendix E – Clinical evidence tables

Cochrane review (Walters, 2018)

Study type	Systematic review
Databases searched	Monthly searches CENTRAL (Cochrane register of studies); PsycINFO Ovid SP 1967 to date; CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) 1937 to date; AMED EBSCO (Allied and Complementary Medicine). Weekly searches MEDLINE Ovid SP 1946 to date; Embase Ovid SP 1974 to date. Handsearches of the proceedings of major respiratory conferences. Supplementary searches MEDLINE (PubMed platform, dates covered 1950 to March 2017); CENTRAL (2017, Issue 3); EMBASE (Embase.com platform, 1947 to July 2014) searches were conducted in previous versions of this review.
Study inclusion criteria	1. Acute exacerbation of COPD? 2. Systemic corticosteroids as intervention? 3. Comparison of short-duration (seven or fewer days) versus longer-duration (longer than seven days) corticosteroid therapy? 4. Randomised controlled trial?
Study exclusion criteria	1. Not different durations of steroids. 2. Not exacerbations of COPD. 3. Not treatment with systemic corticosteroids. 4. Review or other type of article.
Participant inclusion criteria	1. Did the patient have dyspnoea, chronic cough or sputum production? 2. Was there a history of exposure to risk factors including tobacco smoke; occupational dusts and chemicals; and smoke from home cooking and heating fuel? 3. Was a spirometry measurement of the FEV1/FVC ratio less than 0.7 post bronchodilator?
Participant exclusion criteria	Patients with asthma and other lung diseases (e.g. interstitial lung disease, bronchiectasis), unless separate data on participants with COPD alone were available.
Interventions	Short-duration (seven or fewer days) versus longer-duration (longer than seven days) corticosteroid therapy.

Study type	Systematic review
Outcome measures	Treatment failure Relapse Time to re-exacerbation Adverse effects (hyperglycaemia, hypertension, other) Mortality Length of hospitalisation Lung function (FEV1) Arterial blood gases (PaO2, PaCO2) Symptom scores
Risk of bias	Study eligibility and criteria: Low risk of bias Review adhered to pre-defined objectives and eligibility criteria. Eligibility criteria were appropriate for review question, unambiguous and without inappropriate restrictions. Identification and selection of studies: Low risk of bias Monthly searches conducted using Cochrane register of studies. Weekly searches of MEDLINE, Embase, PyscINFO, CINAHL EBSCO and AMED EBSCO. Search strategy was appropriate. Data collection and study appraisal: Low risk of bias Sufficient study characteristics were provided, all relevant study results were collected and a formal risk of bias assessment was conducted. Synthesis and findings: Low risk of bias All relevant identified studies were included in the evidence synthesis and all pre-defined analyses were reported. Sensitivity analysis and funnel plot performed. Minimal bias detected. Heterogeneity addressed where detected. Overall risk of bias: Low Applicability: Directly applicable

Please refer to the evidence tables in the Cochrane review for information about the included studies. The overall risk of bias and directness in Table 6 was determined by the Guideline Updates Team based on the Cochrane review tables.

Table 6: Overall study risk of bias and reason for judgement

Author	Risk of Bias*	Reason	Directness
Chen 2005	Low	All risks low bar reporting bias, which was unclear	Directly applicable
Leuppi 2013	Low	All risks low	Directly applicable
Sayiner 2001	Low	All risks low	Directly applicable
Sirichana 2008	High	Participants, investigators and outcome assessors were not blinded. Of 6/25 participants in one group not completing study,	Directly applicable

		1 participant withdrew and no reason given for other 5.	
Wood-baker 1997	Low	All risks low bar allocation concealment bias, which was unclear	Directly applicable

*Risk of bias in the Cochrane review was scored for 5 types of bias (selection, detection, performance, attrition and reporting). Here all risks of bias have been combined into one final score based on the number of risks and a judgement of the importance of each risk for this review question.

Appendix F – Forest plots

The following plots were based on data from the Cochrane review. However, the dichotomous data plots have been altered to show RR, not OR, and the choice of fixed effect or random effects model is made according to the methods in appendix B. The sensitivity analyses were carried out by NICE Guideline Updates Team using data from the Cochrane review.

Treatment failure

Figure 3: Treatment failure (grouped by mechanism of treatment delivery)

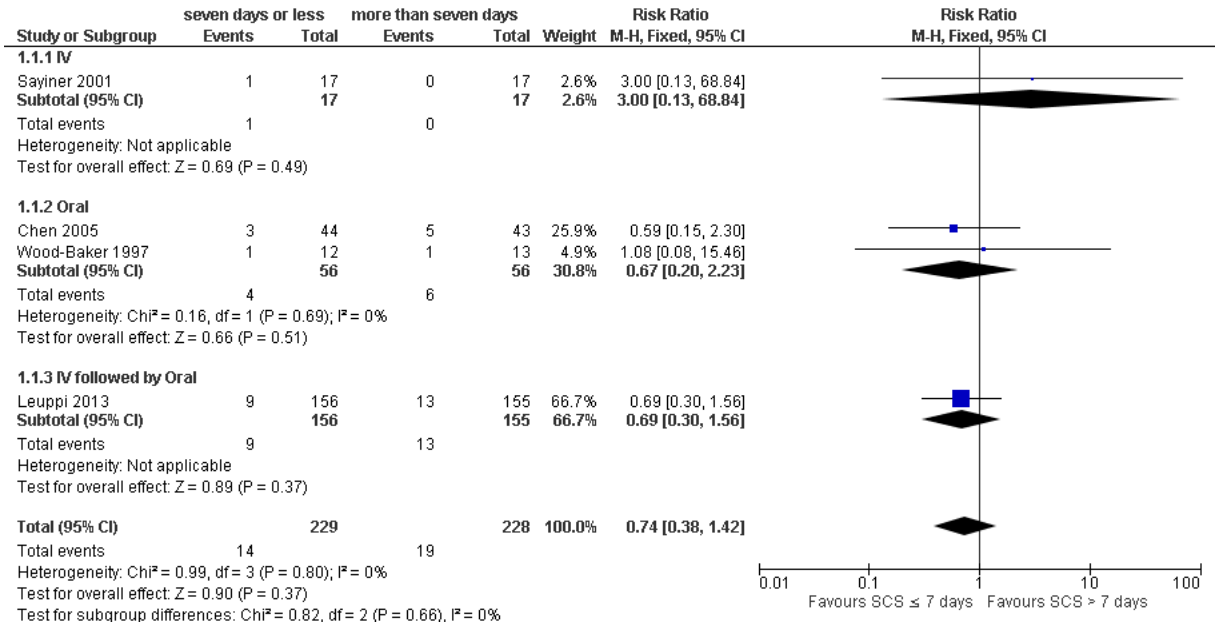
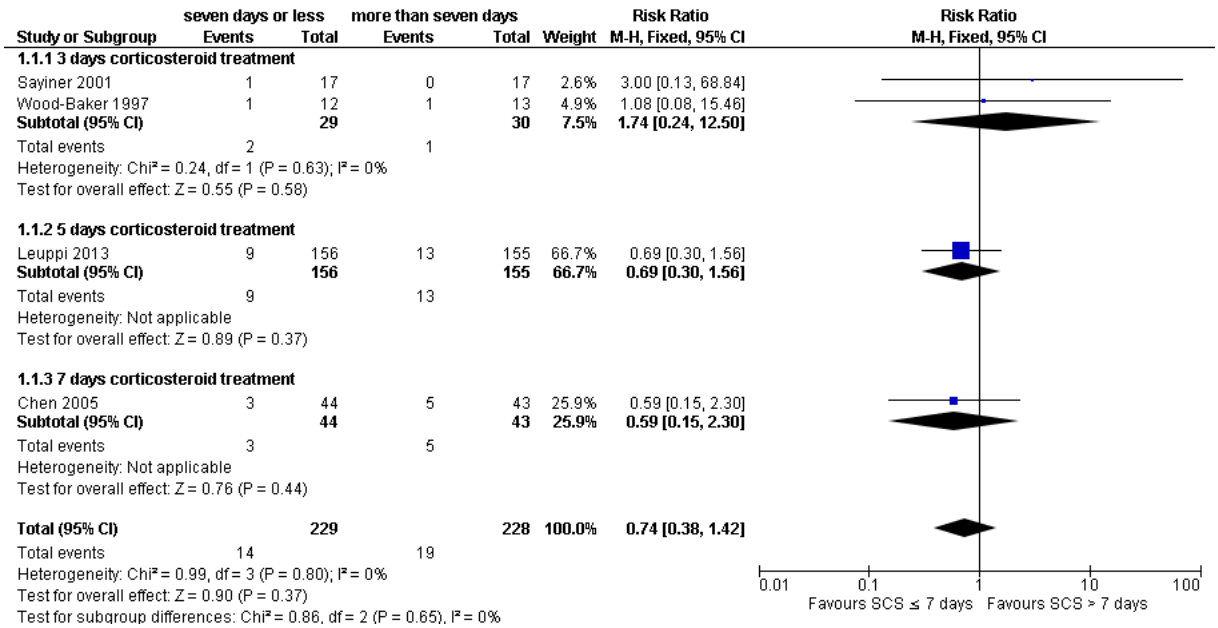


Figure 4: Treatment failure (grouped by length of shorter corticosteroid course)



Relapse

Figure 5: Relapse (grouped by mechanism of treatment delivery)

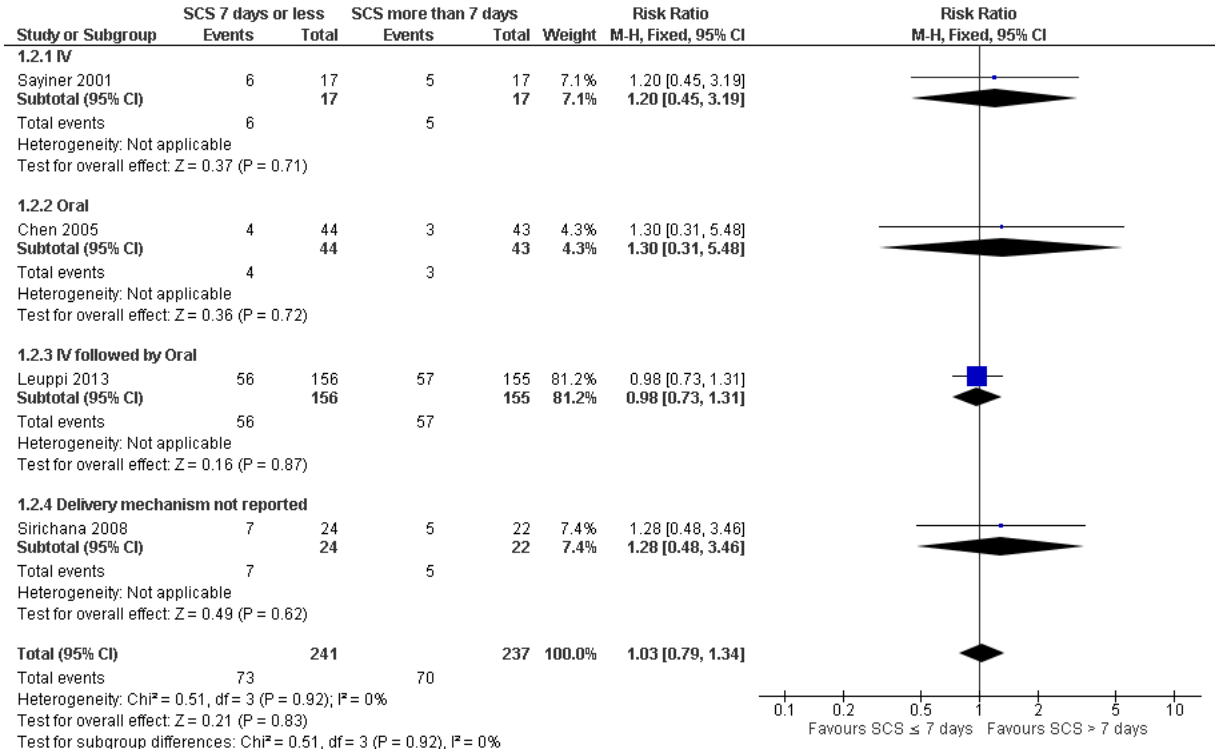


Figure 6: Relapse (grouped by length of shorter corticosteroid course)

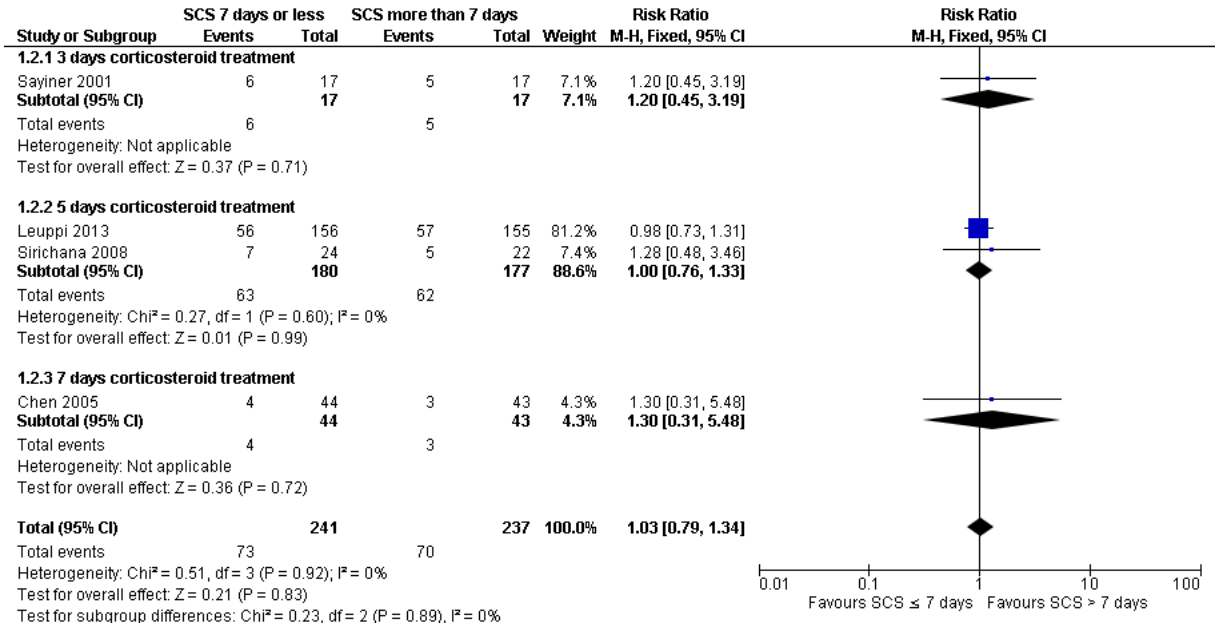


Figure 7: Sensitivity analysis: Removing studies at high risk of bias – Relapse (grouped by mechanism of treatment delivery)

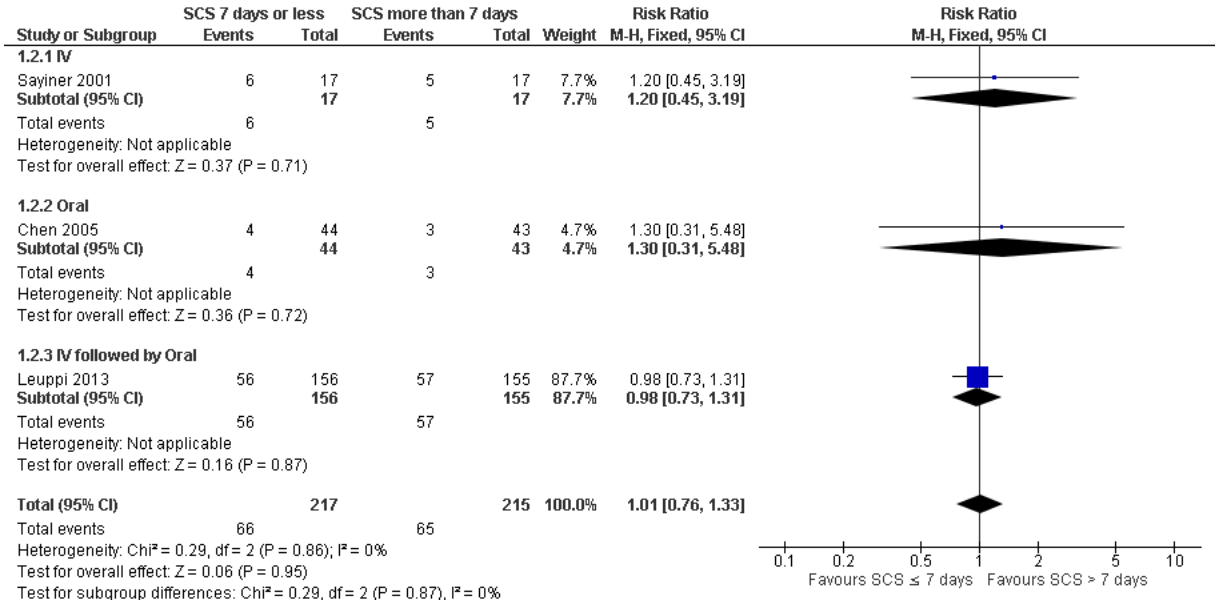
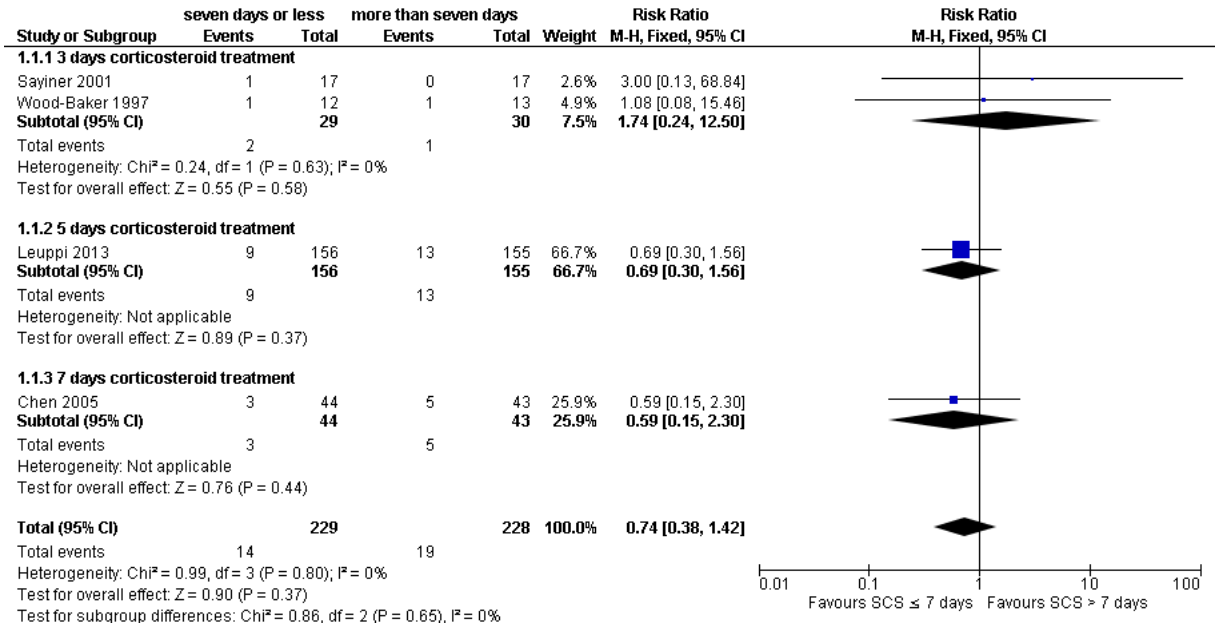
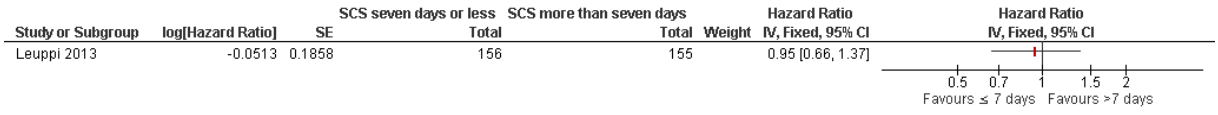


Figure 8: Sensitivity analysis: Removing studies at high risk of bias – Relapse (grouped by length of shorter corticosteroid course)



Time to re-exacerbation

Figure 9: Time to re-exacerbation



Adverse events - hyperglycaemia

Figure 10: Adverse events – hyperglycaemia (grouped by mechanism of treatment delivery)

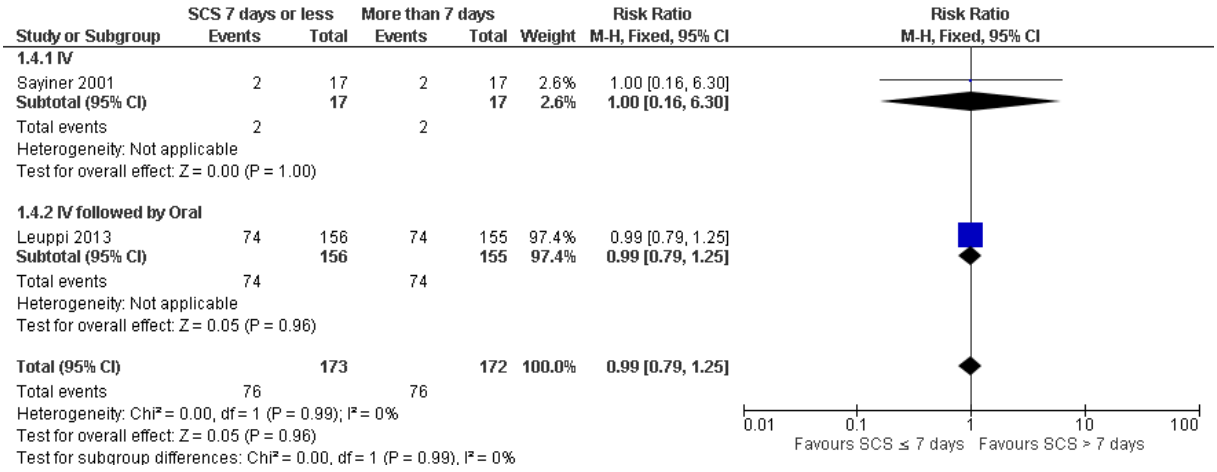
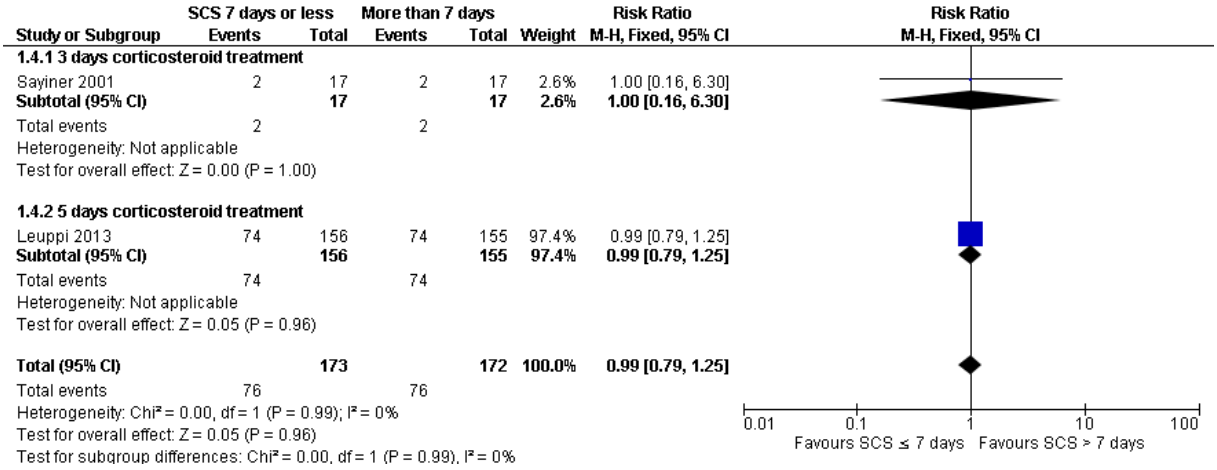
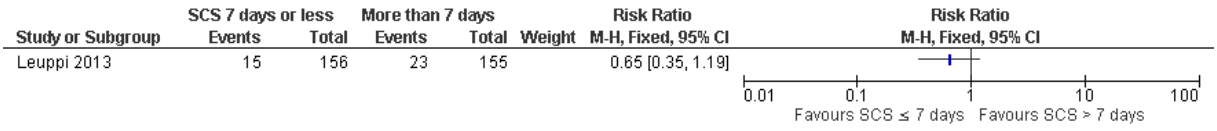


Figure 11: Adverse events - hyperglycaemia (grouped by length of shorter corticosteroid course)



Adverse events - hypertension

Figure 12: Adverse events – hypertension



Other adverse events

Figure 13: Other adverse events – gastrointestinal tract bleeding, symptomatic gastrointestinal reflux, symptoms of congenital heart failure or ischaemic heart disease, sleep disturbance, fractures, depression (grouped by mechanism of treatment delivery)

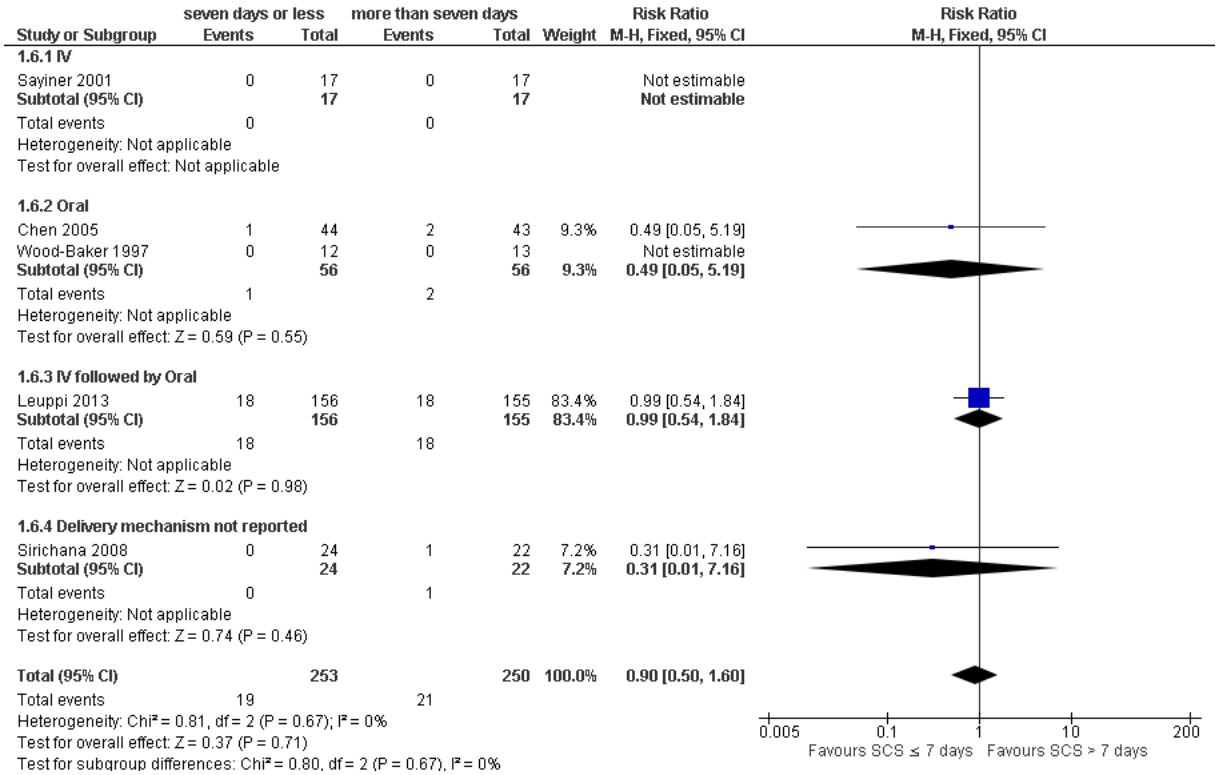


Figure 14: Other adverse events – gastrointestinal tract bleeding, symptomatic gastrointestinal reflux, symptoms of congenital heart failure or ischaemic heart disease, sleep disturbance, fractures, depression (grouped by length of shorter corticosteroid course)

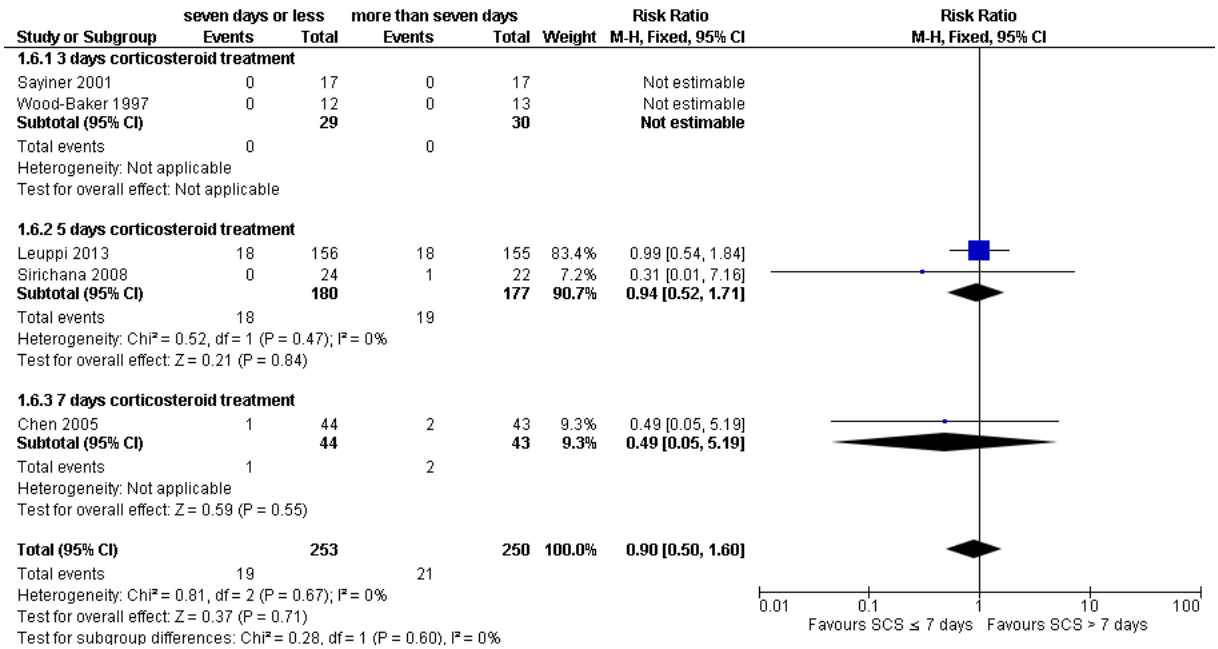


Figure 15: Sensitivity analysis: Removing studies at high risk of bias - Other adverse events – gastrointestinal tract bleeding, symptomatic gastrointestinal reflux, symptoms of congenital heart failure or ischaemic heart disease, sleep disturbance, fractures, depression (grouped by mechanism of treatment delivery)

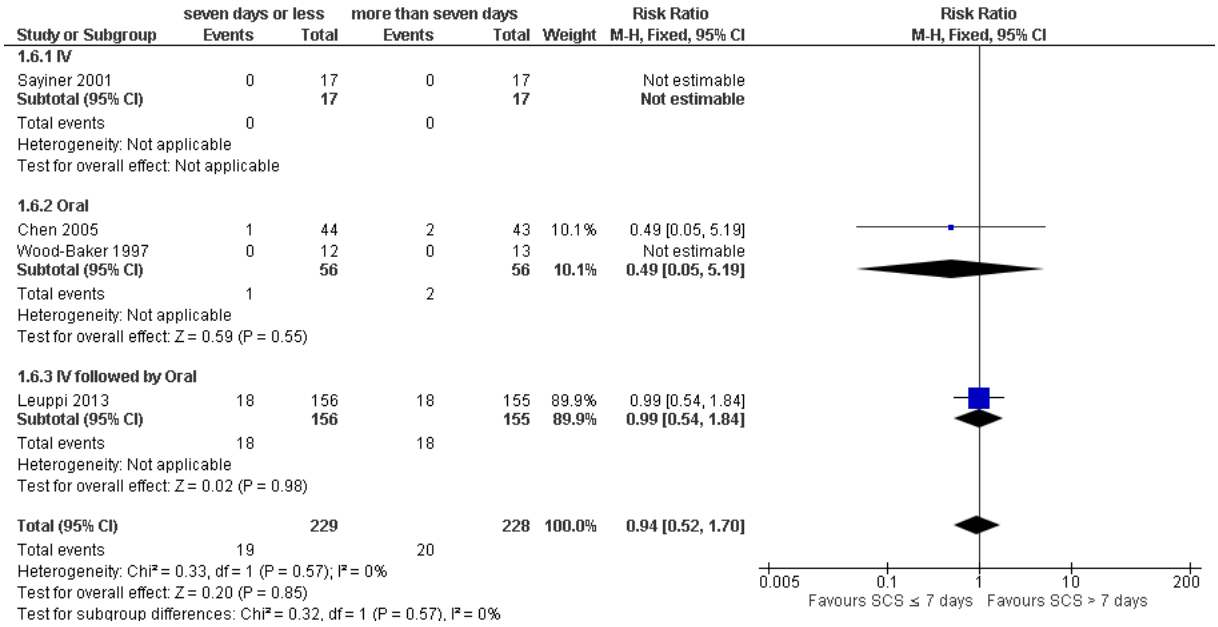
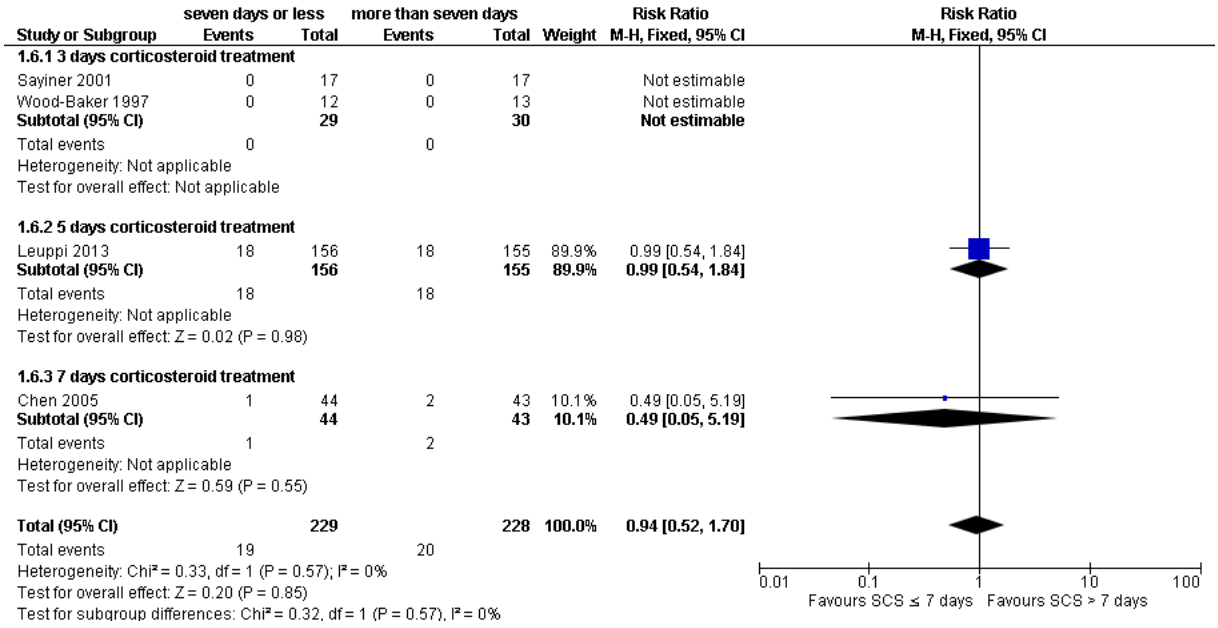


Figure 16: ***Sensitivity analysis: Removing studies at high risk of bias - Other adverse events – gastrointestinal tract bleeding, symptomatic gastrointestinal reflux, symptoms of congenital heart failure or ischaemic heart disease, sleep disturbance, fractures, depression (grouped by mechanism of treatment delivery)***



Mortality

Figure 17: Mortality (grouped by mechanism of treatment delivery)

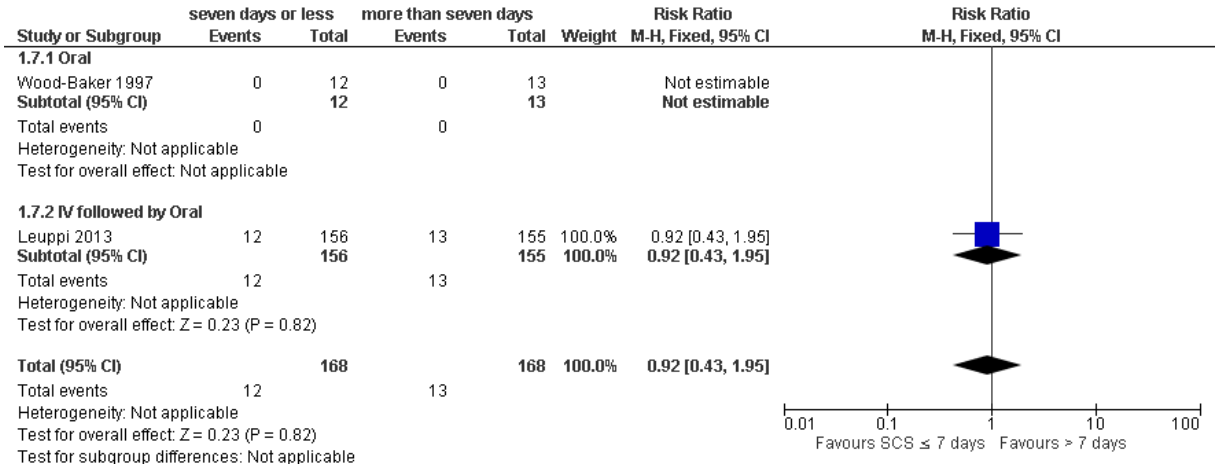
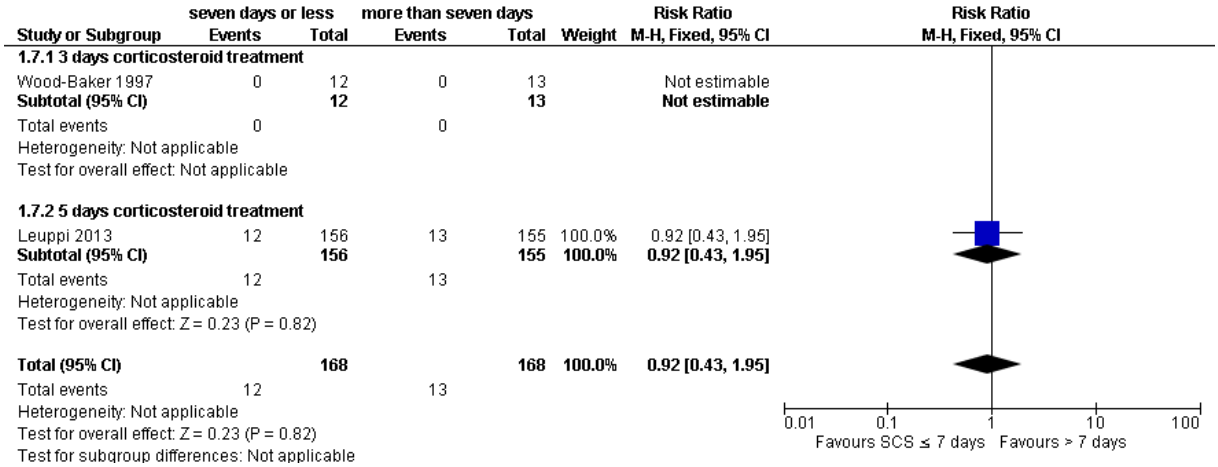


Figure 18: Mortality (grouped by length of shorter corticosteroid course)



Length of hospitalisation

Figure 19: Length of hospitalisation (grouped by mechanism of treatment delivery)

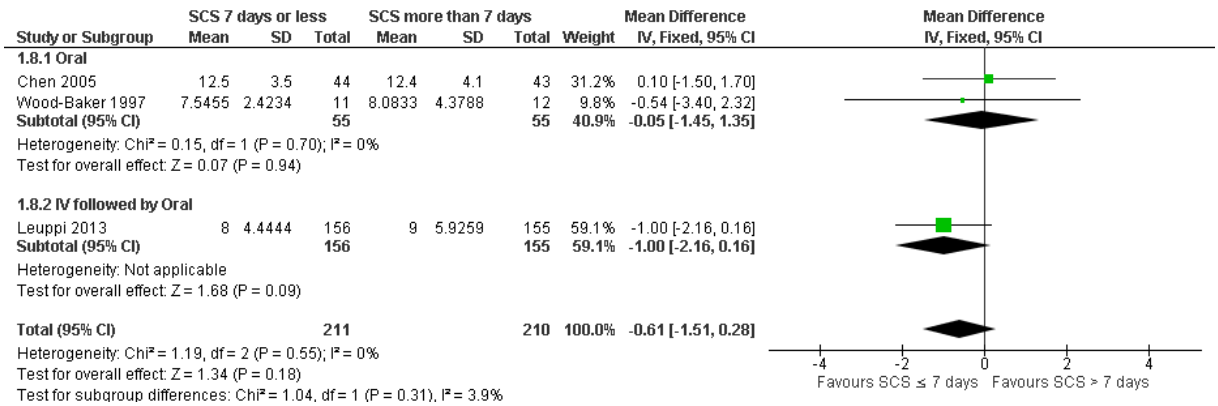
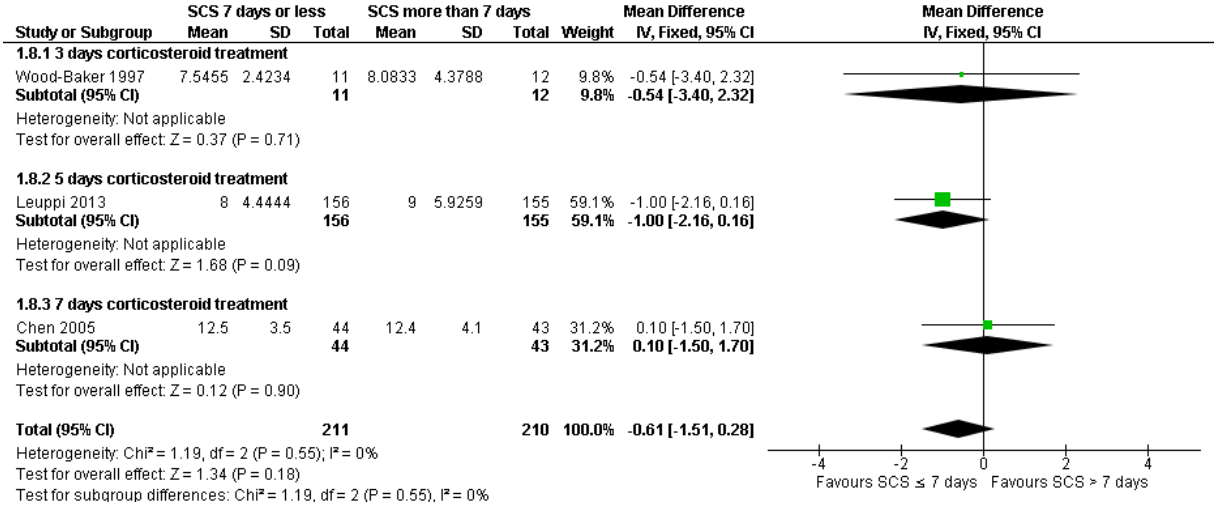


Figure 20: Length of hospitalisation (grouped by length of shorter corticosteroid course)



FEV1 (L) (Early)

Figure 21: FEV1 (L) (Early) (grouped by mechanism of treatment delivery)

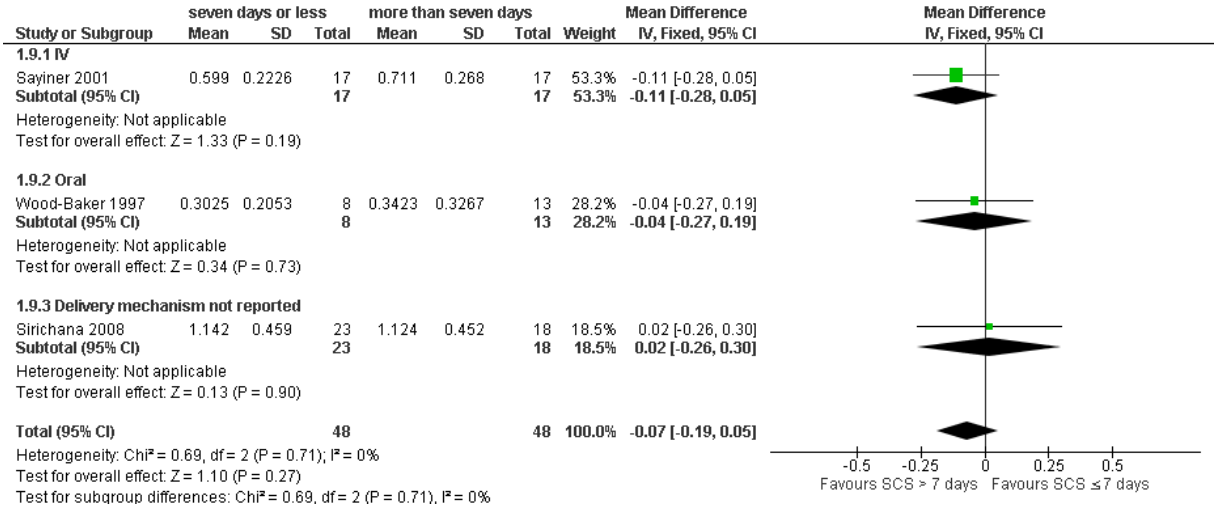


Figure 22: FEV1 (L) (Early) (grouped by length of shorter corticosteroid course)

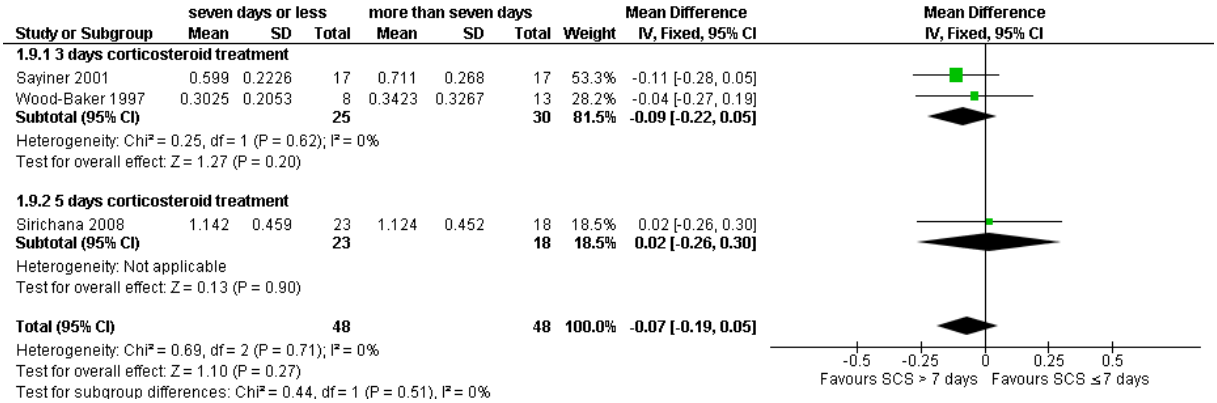


Figure 23: Sensitivity analysis: removing studies at high risk of bias - FEV1 (L) (Early) (grouped by mechanism of treatment delivery)

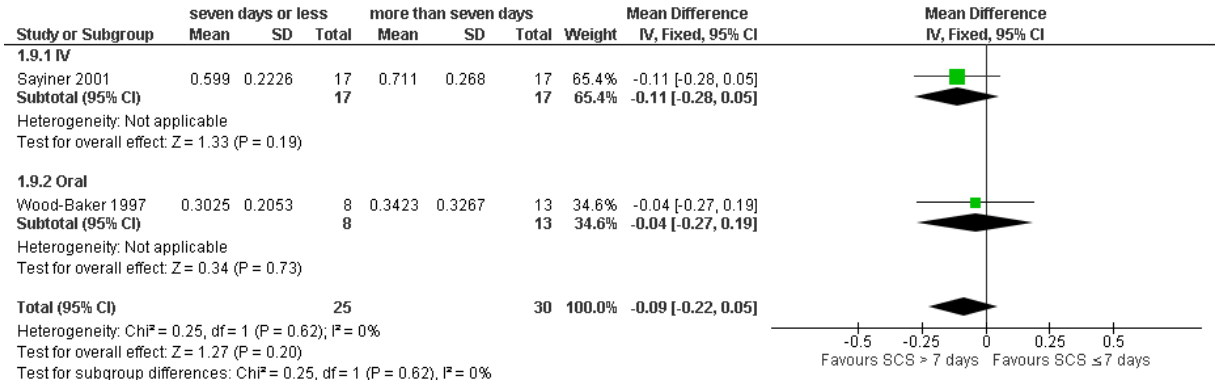
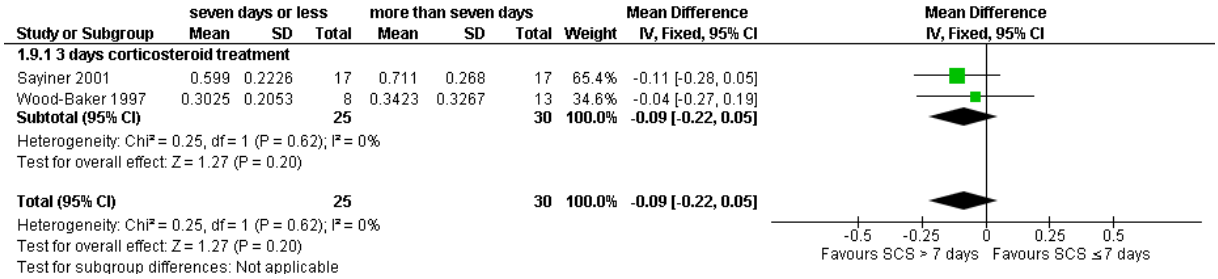
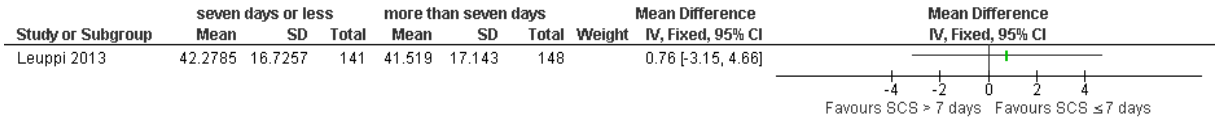


Figure 24: Sensitivity analysis: removing studies at high risk of bias - FEV1 (L) (Early) (grouped by length of shorter corticosteroid course)



FEV1 % predicted (6 days)

Figure 25: FEV1 % predicted (6 days)



FEV1 (L) (End of treatment)

Figure 26: FEV1 (L) (End of treatment) (grouped by mechanism of treatment delivery)

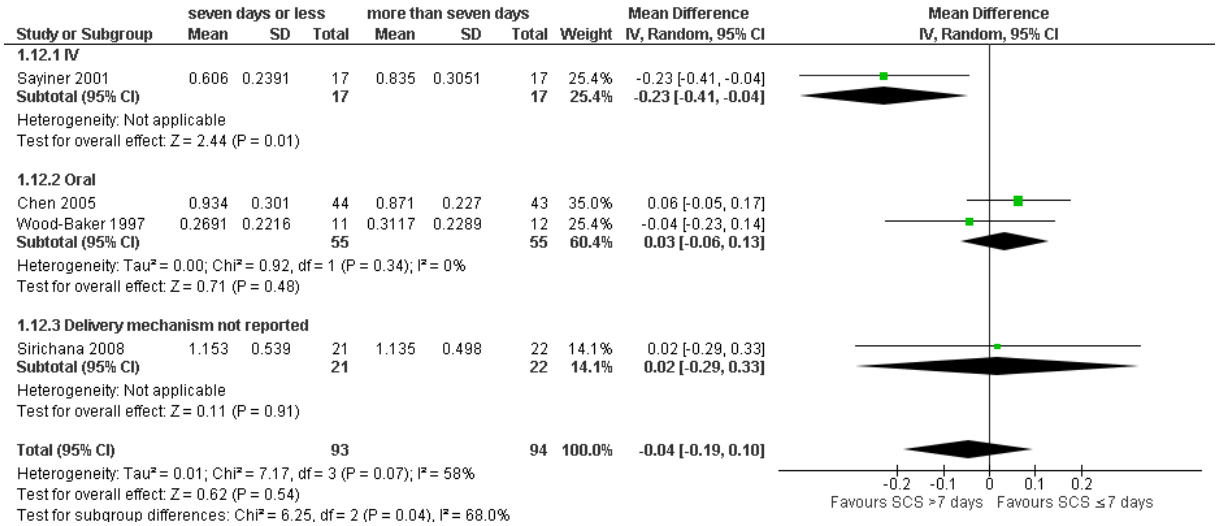


Figure 27: FEV1 (L) (End of treatment) (grouped by length of shorter corticosteroid course)

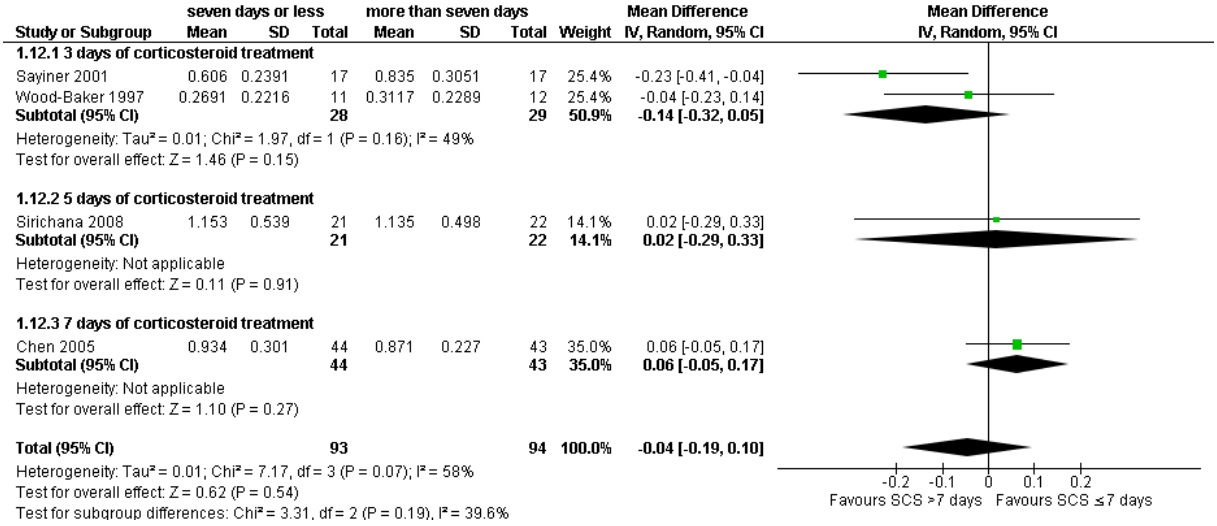


Figure 28: Sensitivity analysis: removing studies at high risk of bias - FEV_1 (L) (End of treatment) (grouped by mechanism of treatment delivery)

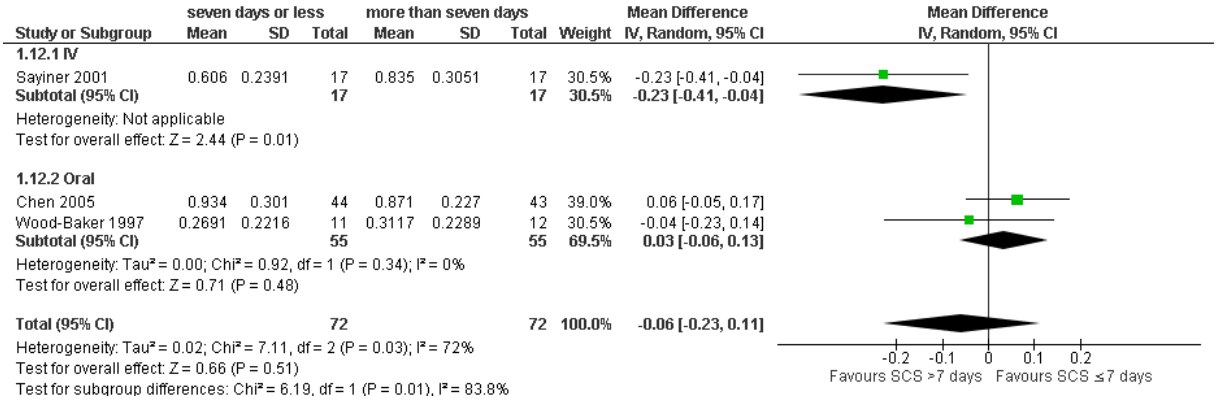
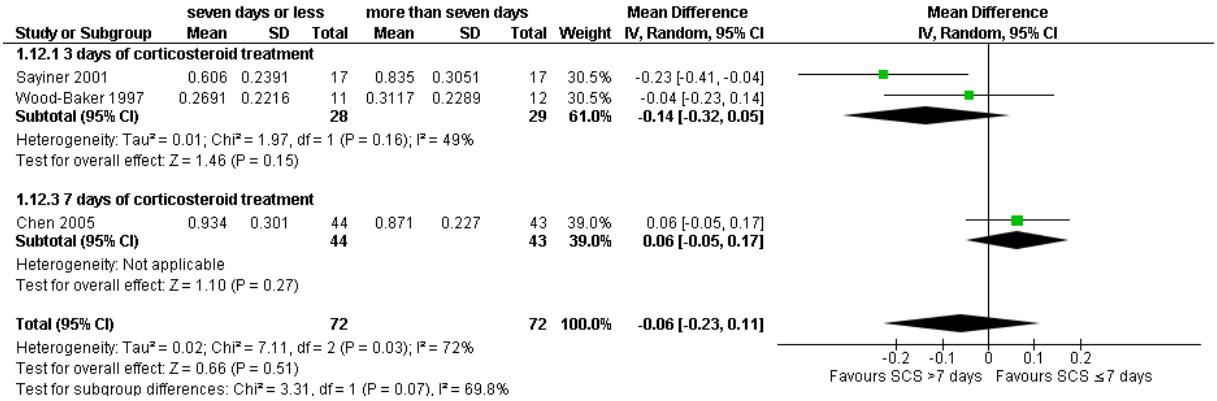
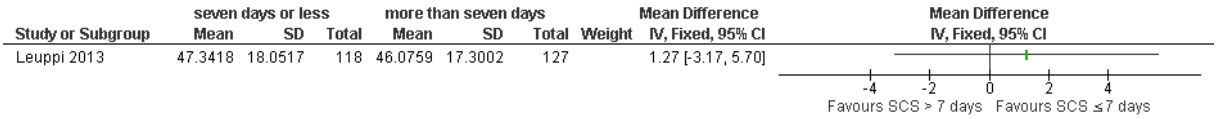


Figure 29: Sensitivity analysis: removing studies at high risk of bias - FEV1 (L) (End of treatment) (grouped by length of shorter corticosteroid course)



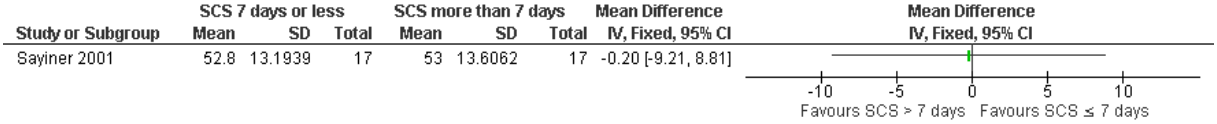
FEV1 % predicted (30 days)

Figure 30: FEV1 % predicted (30 days)



PaO_2 (mmHg) (Early)

Figure 31: PaO_2 (mmHg) (Early)



PaO_2 (mmHg) (End of treatment)

Figure 32: PaO_2 (mmHg) (End of treatment) (grouped by mechanism of treatment delivery)

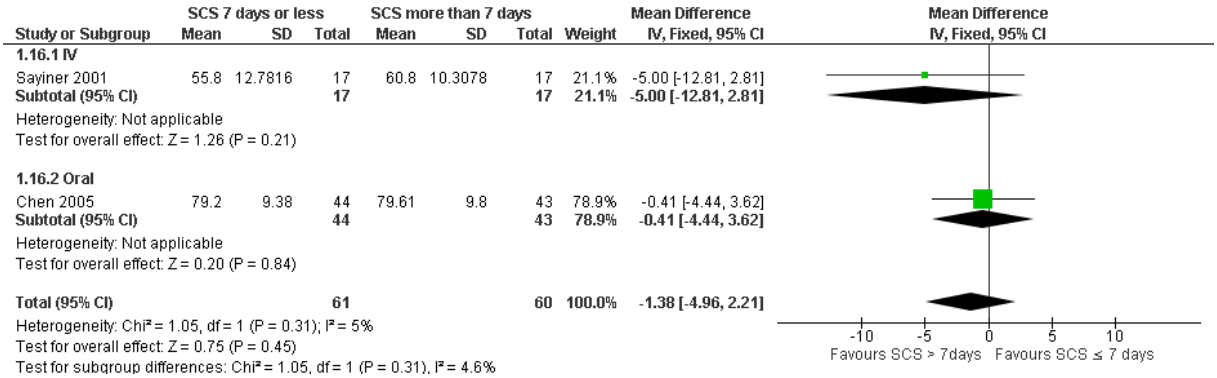
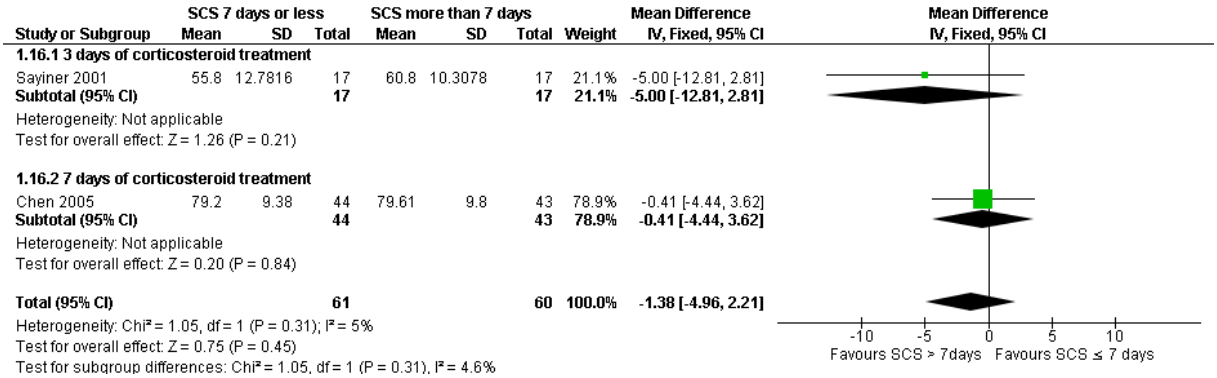
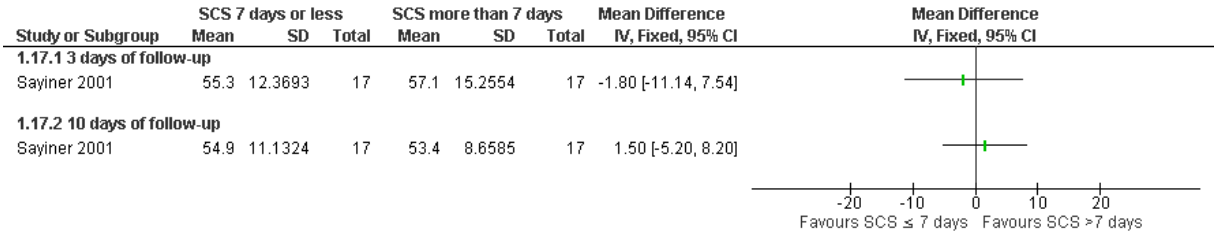


Figure 33: PaO_2 (mmHg) (End of treatment) (grouped by length of shorter corticosteroid course)



$PaCO_2$(mmHg)

Figure 34: $PaCO_2$ (mmHg) (grouped by days of follow-up)



Symptoms – Breathlessness (Early)

Figure 35: Symptoms – Breathlessness (Early) (grouped by mechanism of treatment delivery)

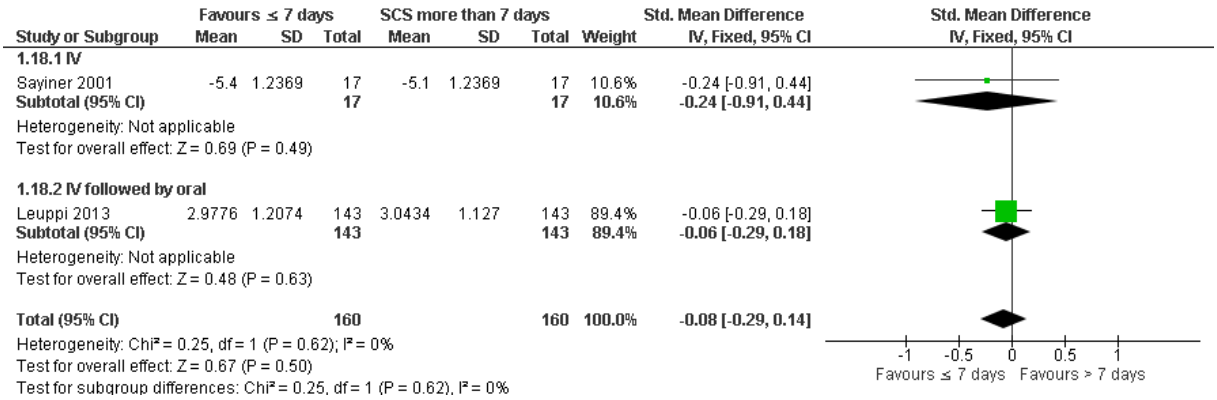
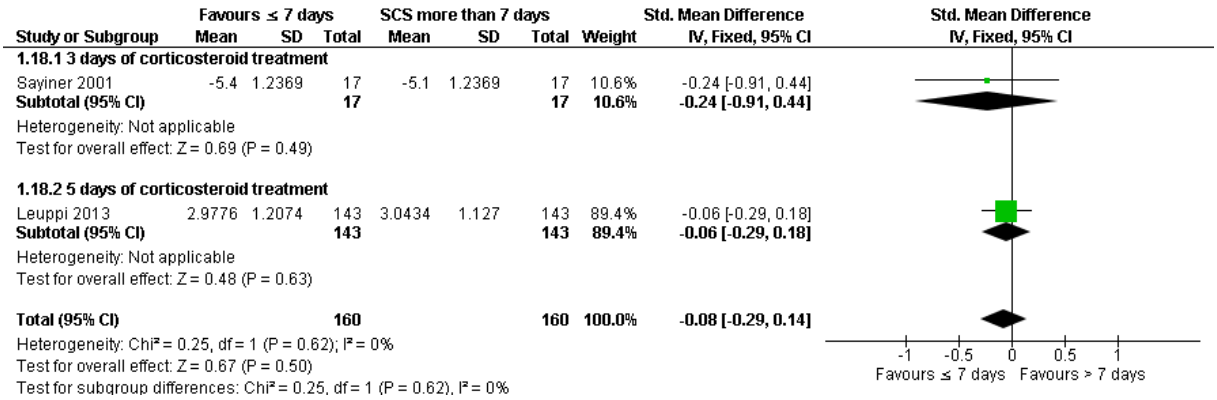


Figure 36: Symptoms - Breathlessness (Early) (grouped by length of shorter corticosteroid course)



Symptoms – Breathlessness (15 days)

Figure 37: Symptoms – Breathlessness (15 days) (grouped by mechanism of treatment delivery)

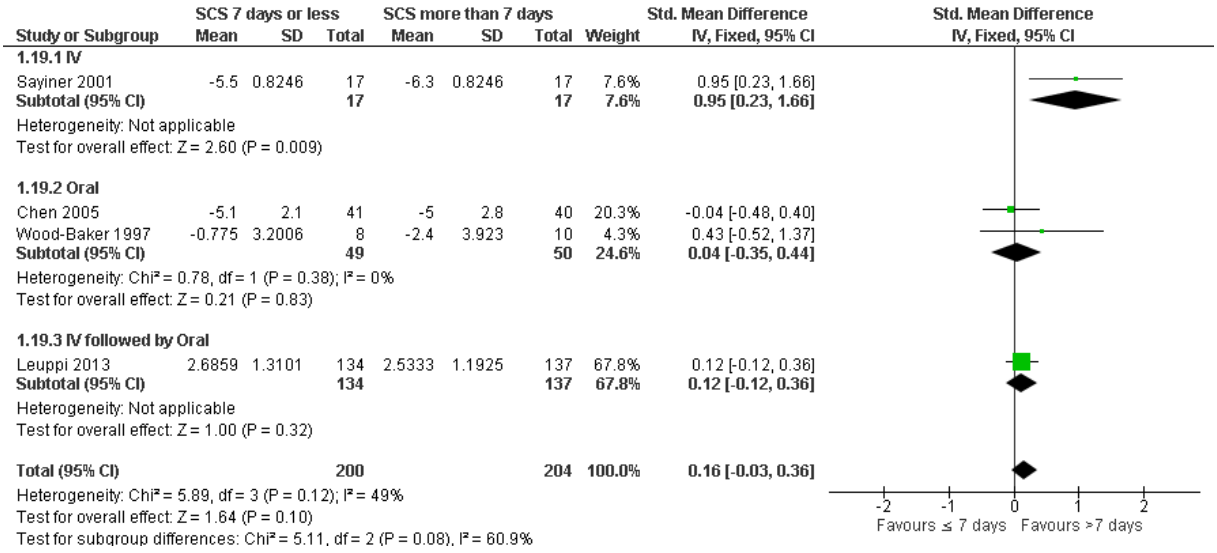


Figure 38: Symptoms - Breathlessness (15 days) (grouped by length of shorter corticosteroid course, 3 days vs 5 days vs 7 days)

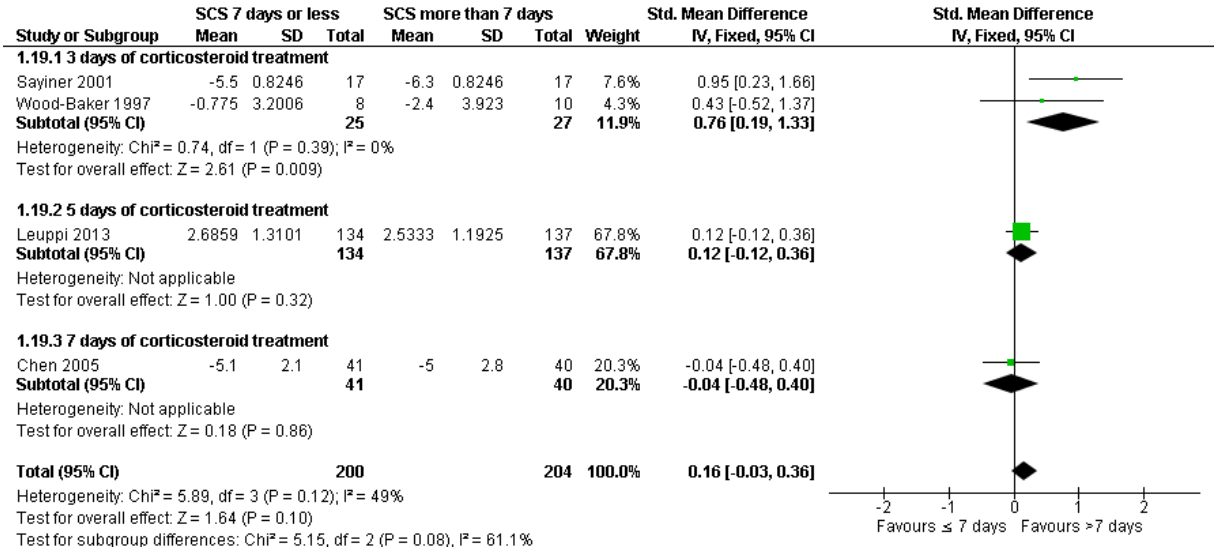
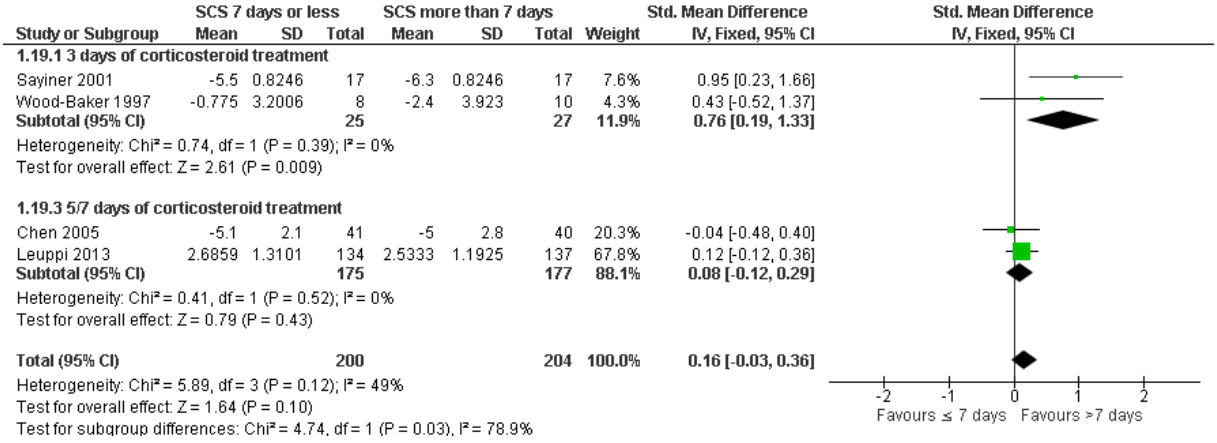
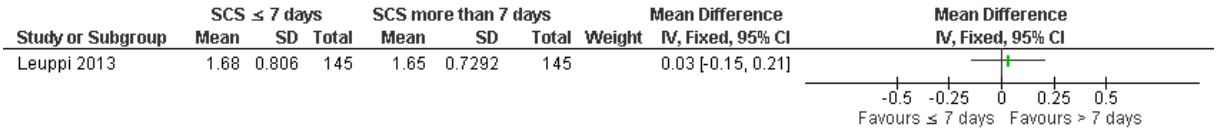


Figure 39: Symptoms - Breathlessness (15 days) (grouped by length of shorter corticosteroid course, 3 days vs 5/7 days)



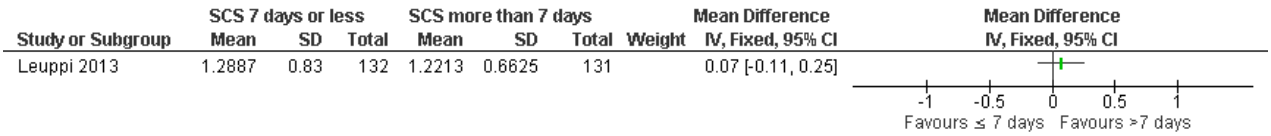
Quality of life – Overall (6 days)

Figure 40: Quality of life - Overall (6 days)



Quality of life – Overall (30 days)

Figure 41: Quality of life - Overall (30 days)



Appendix G – GRADE tables

The following GRADE tables were completed by the NICE Guideline Updates Team tables are based on evidence on effect sizes from the Cochrane review (Walters et al. 2018). However, the dichotomous data has been altered to show RR, not OR, and the choice of fixed effect or random effects model is made according to the methods in appendix B.

Systemic corticosteroids for 7 or fewer days compared to systemic corticosteroids for longer than 7 days

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Treatment failure (events) (RR <1 Favours shorter treatment)										
4 studies	RCT	457	RR 0.74 (0.38, 1.42)	8.33 per 100	6.17 per 100 (3.21, 11.87)	Not serious	Not serious	Not serious	Very serious[1]	Low
Relapse (events) (RR <1 Favours shorter treatment)										
4 studies	RCT	478	RR 1.03 (0.79, 1.34)	29.54 per 100	30.39 per 100 (23.27, 39.69)	Not serious	Not serious	Not serious	Very serious[1]	Low
Sensitivity analysis: Removing studies at high risk of bias - Relapse										
3 studies	RCT	432	RR 1.01 (0.76, 1.33)	30.23 per 100	30.49 per 100 (23.11, 40.23)	Not serious	Not serious	Not serious	Very serious[1]	Low
Time to re-exacerbation (events) (HR <1 Favours shorter treatment)										
1 Study (Leuppi 2013)	RCT	311	HR 0.95 (0.66, 1.37)	-	-	Not serious	Not serious	N/A	Serious[2]	Moderate
Adverse events – hyperglycaemia (RR <1 Favours shorter treatment)										
2 studies	RCT	345	RR 0.99 (0.79, 1.25)	44.19 per 100	43.91 per 100 (34.81, 55.39)	Not serious	Not serious	Not serious	Very serious[1]	Low
Adverse events – hypertension (RR <1 Favours shorter treatment)										
1 Study (Leuppi 2013)	RCT	311	RR 0.65 (0.35, 1.19)	14.84 per 100	9.65 per 100 (5.19, 17.66)	Not serious	Not serious	N/A	Serious[3]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Other adverse events – gastrointestinal tract bleeding, symptomatic gastrointestinal reflux, symptoms of congenital heart failure or ischaemic heart disease, sleep disturbance, fractures, depression (RR <1 Favours shorter treatment)										
5 studies	RCT	503	RR 0.90 (0.50, 1.60)	8.40 per 100	7.53 per 100 (4.22, 13.44)	Not serious	Not serious	Not serious	Very serious[1]	Low
Sensitivity analysis: Removing studies at high risk of bias - Other adverse events – gastrointestinal tract bleeding, symptomatic gastrointestinal reflux, symptoms of congenital heart failure or ischaemic heart disease, sleep disturbance, fractures, depression										
4 studies	RCT	457	RR 0.94 (0.52, 1.70)	8.77 per 100	8.27 per 100 (4.57, 14.96)	Not serious	Not serious	Not serious	Very serious[1]	Low
Mortality (RR <1 Favours shorter treatment)										
2 studies	RCT	336	RR 0.92 (0.43, 1.95)	7.74 per 100	7.1 per 100 (3.34, 15.06)	Not serious	Not serious	N/A[4]	Serious[2]	Moderate
Length of hospitalisation (MD <0 Favours shorter treatment)										
3 studies	RCT	421	MD -0.61 (-1.51, 0.28)	-	-	Not serious	Not serious	Not serious	Serious[2]	Moderate
FEV1 (L) (Early) (MD <0 Favours shorter treatment)										
3 studies	RCT	96	MD -0.07 (-0.19, 0.05)	-	-	Not serious	Not serious	Not serious	Serious[9]	Moderate
Sensitivity analysis: removing studies at high risk of bias - FEV1 (L) (Early)										
2 studies	RCT	55	MD -0.09 (-0.22, 0.05)	-	-	Not serious	Not serious	Not serious	Serious[9]	Moderate
FEV1 % predicted (6 days) (MD <0 Favours longer treatment)										
1 study (Leuppi 2013)	RCT	289	MD 0.76 (-3.15, 4.66)	-	-	Not serious	Not serious	N/A	Serious[2]	Moderate
FEV1 (L) (End of treatment) Pooled result (MD <0 Favours longer treatment)										
4 studies	RCT	187	MD -0.04 (-0.19, 0.10)	-	-	Not serious	Not serious	Serious[5]	Serious[9]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Subgroup analysis: FEV1 (L) (End of treatment) – IV **(MD <0 Favours longer treatment)**										
1 study (Sayiner 2001)	RCT	34	MD -0.23 (-0.41, -0.04)	-	-	Not serious	Not serious	N/A	Serious[9]	Moderate
Subgroup analysis: FEV1 (L) (End of treatment) – Oral **(MD <0 Favours longer treatment)**										
2 studies	RCT	110	MD 0.03 (-0.06, 0.13)	-	-	Not serious	Not serious	Not serious	Serious[9]	Moderate
Subgroup analysis: FEV1 (L) (End of treatment) - Delivery mechanism not reported **(MD <0 Favours longer treatment)**										
1 study (Sirichana 2008)	RCT	43	MD 0.02 (-0.29, 0.33)	-	-	Very serious[6]	Not serious	N/A	Very serious[10]	Very low
Sensitivity analysis: removing studies at high risk of bias - FEV1 (L) (End of treatment) **(MD <0 Favours longer treatment)**										
3 studies	RCT	144	MD -0.06 (-0.23, 0.11)	-	-	Not serious	Not serious	Very serious[7]	Very serious[10]	Very low
FEV1 % predicted (30 days) (MD <0 Favours longer treatment)										
1 Study (Leuppi 2013)	RCT	245	MD 1.27 (-3.17, 5.70)	-	-	Not serious	Not serious	N/A	Serious[2]	Moderate
PaO_2 (mmHg) (Early) (MD <0 Favours longer treatment)										
1 study (Sayiner 2001)	RCT	34	MD -0.20 (-9.21, 8.81)	-	-	Not serious	Not serious	N/A	Serious[2]	Moderate
PaO_2 (mmHg) (End of treatment) (MD <0 Favours longer treatment)										
2 studies	RCT	121	MD -1.38 (-4.96, 2.21)	-	-	Not serious	Not serious	Not serious	Serious[2]	Moderate
$PaCO_2$ (mmHg) 3 days of follow up (MD <0 Favours shorter treatment)										
1 study (Sayiner 2001)	RCT	34	MD -1.80 (-11.14, 7.54)	-	-	Not serious	Not serious	N/A	Serious[2]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
$PaCO_2$ (mmHg) 10 days of follow up (MD <0 Favours shorter treatment)										
1 study (Sayiner 2001)	RCT	34	MD 1.50 (-5.20, 8.20)	-	-	Not serious	Not serious	N/A	Serious[2]	Moderate
Symptoms – Breathlessness (Early) (SMD <0 Favours shorter treatment)										
2 studies	RCT	320	*SMD -0.08 (-0.29, 0.14)* MD -0.14 (-0.49, 0.24)*	-	-	Not serious	Not serious	Not serious	Not serious	High
Symptoms – Breathlessness (15 days) Pooled result (SMD <0 Favours shorter treatment)										
4 studies	RCT	404	*SMD 0.16 (-0.03, 0.36)* MD 0.27 (-0.05, 0.61)*	-	-	Not serious	Not serious	Serious[5]	Not serious	Moderate
Subgroup analysis: Symptoms - Breathlessness (15 days) – 3 days (SMD <0 Favours longer treatment)										
2 studies	RCT	52	SMD 0.76 (0.19, 1.33) MD 1.29 (0.32, 2.25)*	-	-	Not serious	Not serious	Not serious	Serious[8]	Moderate
Subgroup analysis: Symptoms - Breathlessness (15 days) – 5/7 days (SMD <0 Favours longer treatment)										
2 studies	RCT	352	SMD 0.08 (-0.12, 0.29) MD 0.13 (-0.20, 0.49)*	-	-	Not serious	Not serious	Not serious	Not serious	High
Quality of life - Overall (6 days) (MD <0 Favours shorter treatment)**										
1 study (Leuppi 2013)	RCT	290	MD 0.03 (-0.15, 0.21)	-	-	Not serious	Not serious	N/A	Not serious	High

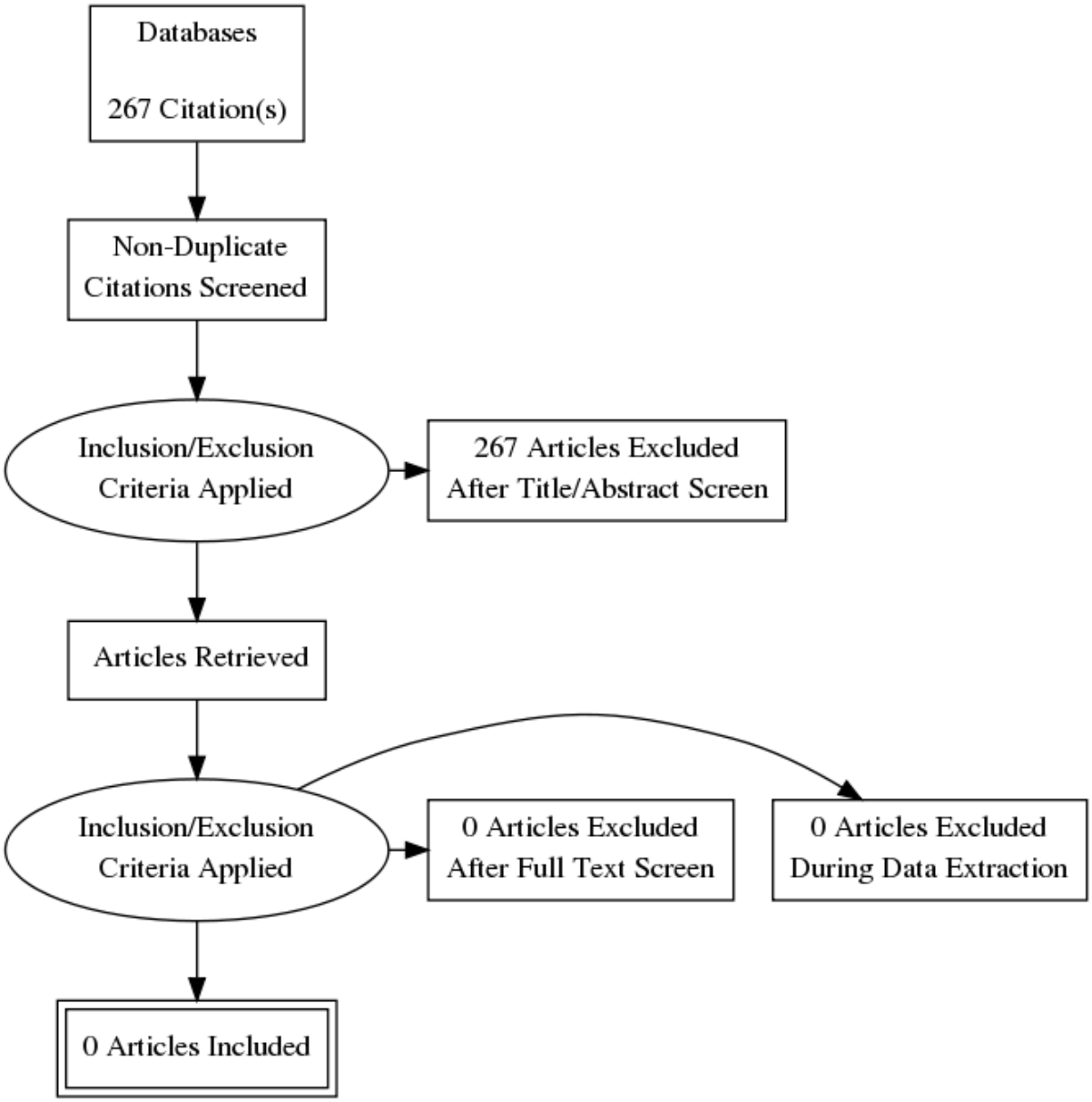
No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Quality of life - Overall (30 days) (MD <0 Favours shorter treatment)**										
1 study (Leuppi 2013)	RCT	263	MD 0.07 (-0.11, 0.25)	-	-	Not serious	Not serious	N/A	Not serious	High

* SMD converted to MD on the BORG scale by multiplying by the pooled SD (1.693579) from the studies included in the 15 day breathlessness meta-analysis

** QoL measure based on a bronchitis-associated quality-of-life score from Evans et al. 2002 [Lancet]

1. 95% confidence interval crosses both ends of the defined MID interval (0.8, 1.25)
2. 95% confidence intervals cross line of no effect
3. 95% confidence interval crosses one end of the defined MID interval (0.8, 1.25)
4. Inconsistency was non-applicable as one study reported 0 events and therefore did not contribute to the meta-analysis
5. I^2 of ≥33.3%
6. >33.3% of studies by weight in the meta-analysis were at a high risk of bias
7. I^2 of ≥66.7%
8. 95% confidence interval crosses one end of the defined MID interval (-2,2)
9. 95% confidence interval crosses one end of the defined MID interval (-0.1, 0.1)
10. 95% confidence interval crosses both ends of the defined MID interval (-0.1, 0.1)

Appendix H – Economic evidence study selection



Appendix I – Excluded studies

Clinical studies

Study	Reason for exclusion
Engel B; Schindler C; Leuppi JD; Rutishauser J, Predictors of re-exacerbation after an index exacerbation of chronic obstructive pulmonary disease in the REDUCE randomised clinical trial, Swiss medical weekly, 147, w14439, 2017	Secondary publication of an included study that does not provide any additional relevant information [Post-HOC analysis of REDUCE trial looking at prognosis]

Appendix J – References

Included clinical studies

Systematic review

Walters JAE; Tan DJ; White CJ; Wood-Baker R. Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD006897. DOI: 10.1002/14651858.CD006897.pub4.

RCTs

Included in meta-analysis

Chen G; Xie CM; Luo YF. [The effects and therapeutic duration of oral corticosteroids in patients with acute exacerbation of chronic obstructive pulmonary diseases]., Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases, 31, 8, 577-580, 2008

Leuppi JD; Schuetz P; Bingisser R; Bodmer M; Briel M; Drescher T; Duerring U; Henzen C; Leibbrandt Y; Maier S; Miedinger D; Müller B; Scherr A; Schindler C; Stoeckli R; Viatte S; von Garnier C; Tamm M; Rutishauser J, Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial., JAMA, 309, 21, 2223-2231, 2013

Sayiner A; Aytemur ZA; Cirit M; Unsal I, Systemic glucocorticoids in severe exacerbations of COPD., Chest, 119, 3, 726-730, 2001

Sirichana W, Sittipunt C, Kawkitinarong K WS, Comparison between 5 days and 10 days of prednisolone in treatment of acute exacerbation of chronic obstructive pulmonary disease. Respirology, 13 (Suppl 5), A120 [012-01], 2008

Wood-Baker R; Wilkinson J; Pearce M RG, A double-blind, randomised, placebo-controlled trial of corticosteroids for acute exacerbations of chronic obstructive pulmonary disease.]. Australian & New Zealand Journal of Medicine, 28, 262, 1997

Not included in meta-analysis

Gomaa M; Faramawy M IH; Duration of systemic corticosteroids treatment in COPD exacerbations., European Respiratory Society 18th Annual Congress; 2008 Oct 3-7, P3601, 2008

Rahman M; Abdullah A; Mamun SM HM, Role of 7-day and 14-day courses of oral prednisolone treatment in acute exacerbation of COPD. Chest, 839s-a, 2004

Salam T; Akers SM; Lotano R; Arnold GK; Bartter T; Pratter MR EA, Optimal duration of corticosteroid therapy in the treatment of exacerbations of chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine, 157 (3 Suppl), A801, 1998