Cochrane
Library

Cochrane Database of Systematic Reviews

Inhaled corticosteroids for cystic fibrosis (Review)

Balfour-Lynn IM, Welch K, Smith S

Balfour-Lynn IM, Welch K, Smith S.
Inhaled corticosteroids for cystic fibrosis.
Cochrane Database of Systematic Reviews 2019, Issue 7. Art. No.: CD001915.
DOI: [10.1002/14651858.CD001915.pub6](https://doi.org/10.1002/14651858.CD001915.pub6).

www.cochranelibrary.com

Inhaled corticosteroids for cystic fibrosis (Review)

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	7
OBJECTIVES	8
METHODS	8
RESULTS	11
Figure 1.	11
Figure 2.	14
DISCUSSION	18
AUTHORS' CONCLUSIONS	20
ACKNOWLEDGEMENTS	20
REFERENCES	21
CHARACTERISTICS OF STUDIES	25
DATA AND ANALYSES	41
Analysis 1.1. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 1: Mean absolute FEV1	43
Analysis 1.2. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 2: Mean absolute FEV1	43
Analysis 1.3. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 3: Mean absolute FEV1 (withdrawal study)	43
Analysis 1.4. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 4: Change in % predicted FEV1 post bronchodilator	44
Analysis 1.5. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 5: Change in % predicted FEV1 (withdrawal study)	44
Analysis 1.6. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 6: Mean absolute FVC	44
Analysis 1.7. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 7: Mean absolute FVC (withdrawal study)	44
Analysis 1.8. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 8: Change in % predicted FVC	45
Analysis 1.9. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 9: Change in % predicted FVC (withdrawal study)	45
Analysis 1.10. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 10: Average patient days in hospital	45
Analysis 1.11. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 11: Average patient days on antibiotics	45
Analysis 1.12. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 12: Growth velocity	46
Analysis 1.13. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 13: Growth velocity (withdrawal study)	46
APPENDICES	46
WHAT'S NEW	46
HISTORY	47
CONTRIBUTIONS OF AUTHORS	48
DECLARATIONS OF INTEREST	48
SOURCES OF SUPPORT	48
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	49
INDEX TERMS	49

[Intervention Review]

Inhaled corticosteroids for cystic fibrosis

Ian M Balfour-Lynn¹, Karen Welch², Sherie Smith³

¹Dept. Paediatric Respiratory Medicine, Royal Brompton Hospital, London, UK. ²c/o Cochrane Cystic Fibrosis and Genetic Disorders Review Group, University of Liverpool, Institute in the Park, Liverpool, UK. ³Division of Child Health, Obstetrics & Gynaecology (COG), School of Medicine, University of Nottingham, Nottingham, UK

Contact: Ian M Balfour-Lynn, i.balfourlynn@ic.ac.uk.

Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.

Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 4, 2021.

Citation: Balfour-Lynn IM, Welch K, Smith S. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2019, Issue 7. Art. No.: CD001915. DOI: [10.1002/14651858.CD001915.pub6](https://doi.org/10.1002/14651858.CD001915.pub6).

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

The reduction of lung inflammation is one of the goals of cystic fibrosis therapy. Inhaled corticosteroids are often used in this respect to treat children and adults with cystic fibrosis. The rationale for this is their potential to reduce lung damage arising from inflammation, as well as their effect on symptomatic wheezing. It is important to establish the current level of evidence for the risks and benefits of inhaled corticosteroids, especially in the light of their known adverse effects on growth. This is an update of a previously published review; however, due to the lack of research in this area, we do not envisage undertaking any further updates.

Objectives

To assess the effectiveness of taking regular inhaled corticosteroids compared to not taking them in children and adults with cystic fibrosis.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register, comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings. We requested information from pharmaceutical companies manufacturing inhaled corticosteroids and authors of identified trials.

Date of most recent search of the Group's Trials Register: 19 November 2018.

Selection criteria

Randomised or quasi-randomised trials, published and unpublished, comparing inhaled corticosteroids to placebo or standard treatment in individuals with cystic fibrosis.

Data collection and analysis

Two independent authors assessed methodological quality and risk of bias in trials using established criteria and extracted data using standard pro formas. The quality of the evidence was assessed using the GRADE criteria.

Main results

The searches identified 35 citations, of which 27 (representing 13 trials) were eligible for inclusion. These 13 trials reported the use of inhaled corticosteroids in 525 people with cystic fibrosis aged between 6 and 55 years. One was a withdrawal trial in 171 individuals who were already taking inhaled corticosteroids. Methodological quality and risk of bias were difficult to assess from published information.

Objective measures of airway function were reported in most trials but were often incomplete and reported at different time points. We found no difference in forced expiratory volume in one second (FEV₁) or forced vital capacity (FVC) % predicted in any of the trials, although

the quality of the evidence was low due to risks of bias within the included trials and low participant numbers. We are uncertain whether inhaled corticosteroids result in an improvement in exercise tolerance, bronchial hyperreactivity or exacerbations as the quality of the evidence was very low. Data from one trial suggested that inhaled corticosteroids may make little or no difference to quality of life (low-quality evidence).

Three trials reported adverse effects, but the quality of the evidence is low and so we are uncertain whether inhaled corticosteroids increase the risk of adverse effects. However, one study did show that growth was adversely affected by high doses of inhaled corticosteroids.

Authors' conclusions

Evidence from these trials is of low to very low quality and insufficient to establish whether inhaled corticosteroids are beneficial in cystic fibrosis, but withdrawal in those already taking them has been shown to be safe. There is some evidence they may cause harm in terms of growth. It has not been established whether long-term use is beneficial in reducing lung inflammation, which should improve survival, but it is unlikely this will be proven conclusively in a randomised controlled trial.

PLAIN LANGUAGE SUMMARY

Inhaled corticosteroids for cystic fibrosis

Review question

We reviewed the evidence about the effect of inhaled corticosteroids in people with cystic fibrosis.

Background

Repeated chest infections in people with cystic fibrosis cause inflammation and damage to the lungs which, in the long term, is the most common reason for death. Inhaled corticosteroids are often used to treat inflammation, but may cause some side effects. Some of these side effects are less serious, e.g., oral thrush, but others are more serious, such as reduced growth rate in childhood. This is an update of a previously published review and due to a lack of research in this area, we do not plan any further updates.

Search date

The last search for evidence was on 19 November 2018.

Study characteristics

In this updated review, 13 trials reported the use of inhaled corticosteroids in 525 people with cystic fibrosis. In most of the trials participants started taking steroids or placebo (treatment that appeared the same as the steroids, but did not have any active medicine in it) at the start of the trial, but one trial was a withdrawal trial (171 participants), where everyone was already taking steroids and while half of them carried on, the rest took a placebo, in effect stopping the treatment. Participants were aged between 6 and 55 years; three of the trials were in children only, four in adults only and four were mixed ages; two trials did not describe the ages of the people taking part. The lung function and severity of disease of the participants varied across trials and only two trials gave information about their genetic mutations. All trials took place in Europe. In 10 of the trials, all those taking part remained in the same group up to the end of the trial (either a treatment group or a group receiving no treatment or a placebo), but in three trials they swapped groups halfway through the trial. The trials lasted between three weeks and two years.

Key results

The clinical trials have not been able to prove that inhaled corticosteroids reduce inflammation in the lungs of people with cystic fibrosis. We found no difference in measurements of lung function, exercise tolerance, the reaction of airways to irritation or the number of exacerbations (flare up of symptoms). Generally, it was unclear if inhaled corticosteroids increased the risk of adverse effects, but one trial did show that these drugs can slow down children's growth when used in high doses. Furthermore, results from the withdrawal trial showed that under close supervision of the cystic fibrosis team, it may be safe for people who have been taking inhaled corticosteroids for some time to stop doing so.

Quality of the evidence

We thought the quality of the evidence was low to very low. A lack of information meant we were often not able to judge if the way the trials were designed or run could have affected our confidence in the results. Only three trials gave details of how they made sure people taking part had equal chances of being in the treatment or placebo groups; and only five described how they made sure the people recruiting participants did not know which groups they would be going into. In most cases, we did not think that once the trials started the people taking part or their doctors knew whether they were getting steroids or placebo. However, we did have some concerns that four of the trials had not been published in journals, who would have sent the reports to experts to check for accuracy and we were not sure how this might affect our confidence in the results.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings: inhaled corticosteroids compared with placebo for cystic fibrosis

Inhaled corticosteroids compared with placebo for cystic fibrosis

Patient or population: children and adults with cystic fibrosis

Settings: outpatients

Intervention: inhaled corticosteroids

Comparison: inhaled placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Inhaled corticosteroids				
Lung function: FEV ₁ % predicted (change from baseline) Follow-up: 30 days to 12 months	See comments.		N/A	250 (3)	⊕⊕⊕⊕ low ^{1,2}	Change from baseline in FEV ₁ % predicted measured at different time points across trials, so not possible to combine the data. No significant difference between inhaled corticosteroids and placebo was found in any of the trials.
Lung function: FVC % predicted (change from baseline) Follow-up: 30 days to 12 months	See comments.		N/A	250 (3)	⊕⊕⊕⊕ low ^{1,2}	Change from baseline in FVC % predicted was also measured at different time points across trials precluding the combination of data. No significant difference between inhaled corticosteroids and placebo was demonstrated in any of the trials.
BHR: change in PC ₂₀ values	See comments.		N/A	100 (3)	⊕⊕⊕⊕ very low ^{1,2,3}	Results only reported narratively due to differences in methods of measuring and reporting BHR.

Follow-up: 6 weeks to 6 months						<p>1 trial reported a greater change in histamine dose steps in the budesonide group, MD 1.13% (95% CI 0.01% to 2.26%) (P < 0.05) (Danish Trial 1997).</p> <p>1 trial reported significant increases in mean log PC₂₀ histamine and geometric mean PC₂₀ histamine in the budesonide arm, but no equivalent data or report were given for the placebo arm (Dutch Trial 1995).</p> <p>1 trial found no difference between groups in the change in BHR with methacholine challenge (P = 0.7) (Turkish Trial 2017).</p>
Improvement in exercise tolerance	See comments.		N/A	12 (1)	⊕⊕⊕⊕ very low ^{1,2,3}	<p>Trial used a symptom score (0 - 3; where 0 = no complaints and 3 = severe complaints), mean scores for dyspnoea at rest for budesonide and placebo were 0.38 and 0.54 respectively (P < 0.05), but scores did not differ significantly for dyspnoea during exercise, 0.98 and 0.97 respectively.</p>
Follow-up: 6 weeks						
Respiratory exacerbations: number of days on intravenous antibiotics for respiratory exacerbations	The mean number of days on antibiotics in the control group was 51.3 days.	The mean number of days in hospital in the intervention group was 4.40 days lower (50.40 days lower to 41.64 days higher).	MD -4.40 (-50.40 to 41.64)	17 (1)	⊕⊕⊕⊕ very low ^{2,4}	<p>Trial halted prematurely and results never published in a peer-reviewed journal. Data provided by investigators along with number of days of hospitalisation (which also showed no significant difference between groups) (Canadian Trial 1997).</p> <p>1 further trial (171 participants) narratively reported no difference between groups in IV or oral antibiotic use at 6 months and no difference in time to first exacerbation (CF WISE 2006). Also, 1 trial (29 participants) reported the number of exacerbations and again found no significant difference (Belgian Trial 2007).</p>
Follow-up: 9 months						
Quality of life: change in well-being score	See comments.		N/A	23 (1)	⊕⊕⊕⊕ low ⁵	<p>1 trial reported quality of life and found no significant change in well-being scores between either 6-week treatment period (UK Trial 1997).</p> <p>1 further trial (n = 16) with no analysable data reported a small but significant improvement in cough or dyspnoea in the fluticasone group (Dutch Trial 1995).</p>
Follow-up: 6 weeks						
Adverse effects	See comments.		N/A	295 (5)	⊕⊕⊕⊕ low ⁶	<p>3 trials reported specific adverse effects, but a further 2 reported data we regard as related to adverse effects.</p> <p>1 trial (n = 55) reported 17 adverse events in the budesonide group compared with 13 in the placebo group, but it is unclear whether the numbers reported relate</p>
Follow-up: 6 weeks to 6 months						

to individuals or individual episodes. The budesonide group attended more frequently for outpatient visits than the placebo group, reported hoarseness of voice, oral thrush, haemoptysis, pharyngitis and chest pain ([Danish Trial 1997](#)).

1 UK trial (n = 23) reported 2 treatment-related adverse effects, both in the fluticasone group ([UK Trial 1997](#)).

In 1 trial (n = 171) fewer participants withdrew due to lung-related symptoms in the fluticasone group, RR 0.59 (95% CI 0.12 to 1.48) ([CF WISE 2006](#)).

Also, although growth is reported under "Change in nutritional indices", 1 trial (n = 29) reported significantly impaired growth in the ICS group compared to the placebo group, MD -1.53 cm (95% CI -2.37 cm to -0.69 cm) and participants did not "catch up" height in the 12 months following fluticasone discontinuation. A difference in growth rate of 2.4 cm was reported between groups after 24 months ([Belgian Trial 2007](#)).

1 further trial (n = 17) did not report adverse events as an outcome, but the trial was halted prematurely because of concerns about possible increased frequency of pulmonary colonisation with *Pseudomonas aeruginosa* in participants ([Canadian Trial 1997](#)). Conversely, the Belgian trial reported no increase in the isolation of *P aeruginosa* between the 2 groups of participants ([Belgian Trial 2007](#)).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BHR: bronchial hyperreactivity; **CI**: confidence interval; **FEV₁**: forced expiratory volume in 1 second; **FVC**: forced vital capacity; **ICS**: inhaled corticosteroids; **IV**: intravenous; **MD**: mean difference; **RR**: risk ratio.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

1. Downgraded once due to risk of bias across the included trials, particularly for the domains of randomisation and allocation concealment.
2. Downgraded once due to imprecision from low participant numbers in most of the included trials which would not meet the optimal information size.
3. Downgraded once due to selective reporting or publication bias as the Dutch trial only reported an improvement in the intervention group and did not report data for the placebo group.

4. Downgraded twice due to risk of bias in the single included trial. The randomisation process was unclear and the trial was halted prematurely. The trial results have never been published in a peer-reviewed journal.
5. Downgraded two times; once due to risk of bias within the single included trial for this outcome as the randomisation process was unclear and once due to imprecision as the sample size is small.
6. Downgraded two times; once due to risk of bias in the included trials. Two of the trials reporting this outcome had unclear randomisation processes; and once due to imprecision from low event rates and participant numbers.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a chronic disorder, of autosomal recessive inheritance, which principally affects the respiratory tract, pancreas, gastro-intestinal tract and liver. In the respiratory tract, abnormalities result in mucus plugging of the airways and susceptibility to respiratory tract infection. This leads to neutrophil-dominated airway inflammation with consequent lung damage (bronchiectasis), and eventually respiratory failure and death. Inflammation is also important in the development of the bronchial hyperreactivity (BHR) and airway instability that may be associated with CF. Up to half of people with CF have measurable BHR, which seems unrelated to atopic status (Burdon 1980; Mitchell 1978; Tobin 1980). Although prognosis and survival continue to improve, it is the lung damage which is the single most important factor responsible for premature death. Lung damage also has implications for quality of life, and slowing of the rate of progression of lung disease is an important goal in the management of CF. The search for a suitable anti-inflammatory strategy has gone on for over two decades, but unfortunately there is still no ideal agent available (Balfour-Lynn 2007). Lung inflammation may commence very early in life (Khan 1995), and may be present even in those without clinical manifestations of lung disease (Armstrong 1995) or positive bacterial culture (Balough 1995; Konstan 1994). Although a normal inflammatory response is beneficial to host defence mechanisms, the exaggerated response seen in CF contributes to the morbidity and ultimately the mortality associated with the disease (Hilliard 2005).

Description of the intervention

Corticosteroids (glucocorticoids) are potent non-specific anti-inflammatory agents which have been widely used in a variety of inflammatory disorders. They can be administered topically or systemically, but this review is concerned only with corticosteroids given by the inhaled route.

How the intervention might work

In asthma, inhaled corticosteroids (ICS) reduce BHR and airway inflammation (Barnes 1992; Booth 1995; Djukanovic 1992; van Grunsven 1999) and lead to modest improvements in airway function (Calpin 1997). Although beneficial effects on pulmonary function, but not BHR, have been reported in chronic obstructive pulmonary disease (COPD) (Renkema 1996; Weir 1993), there is proven benefit only in certain aspects of COPD management (NICE 2004). Furthermore, a COPD biopsy study showed that three months of inhaled fluticasone did not reduce the neutrophilic inflammation, despite improvement in symptoms and exacerbation rate (Hattotuwa 2002). The rationale for their use in CF lies in observations that inflammation occurs early in the course of CF and may contribute to lung damage. The Cochrane Review of evidence for the effectiveness of oral corticosteroids in CF concluded that treatment with a prednisolone equivalent dose of 2 mg/kg on alternate days appeared to slow the progression of lung disease but was associated with a high risk of important side effects (Cheng 1999).

Corticosteroids are associated with a wide range of potential adverse effects, all of which tend to be more severe with oral or other systemic preparations (ABPI 1999). Oral administration over prolonged periods may lead to a Cushingoid appearance

with redistribution of fat to the central areas of the body, obesity, muscle wasting, acne, bruising, thinning of the skin and skin striae. High doses can also precipitate or exacerbate impaired glucose metabolism. Prolonged use is associated with reduced bone mineral density and posterior subcapsular cataracts. In children, one of the most important side effects is growth suppression. There are also concerns that substantial inhibition of inflammation could impair innate immunity and make the patient more susceptible to infection (Koehler 2004).

Inhaled preparations of corticosteroids have been developed to maximise effective treatment of lung inflammation and reduce the frequency of harmful effects, but these have not been completely eliminated (Russell 2004). Systemic adverse effects occur with all ICS, although to a lesser degree than seen with oral preparations (Lipworth 1999). These appear to be related to both dose and duration of treatment. In one meta-analysis, an increased risk of adrenal suppression and bone thinning was found at daily doses above 1.5 mg (budesonide equivalent) per day (which equates to above 0.75 mg per day for fluticasone) (Lipworth 1999). Over the last decade there has been increasing concern about the potential effects of ICS on adrenal function, with several case series reporting symptomatic adrenal suppression including hypoglycaemia, coma and even death in asthmatic adults and children taking high-dose (and less often standard-dose) ICS (Drake 2002; Macdessi 2003; Patel 2001; Taylor 1999; Todd 1996; Todd 2002). More recently, there has been a population-based case controlled study suggesting an association of high doses for long duration may be associated with cataracts in those over 40 years old (Smeeth 2003). Other less severe adverse effects include hoarseness of voice and oral candidiasis.

Why it is important to do this review

In 1994, in the UK, 34% of adults with CF surveyed reported that they took inhaled steroids (Walters 1995) and this had risen to 51% in a subsequent survey conducted in 2000 (Walters 2001). National databases showed there to have been an increase in prescribing and use both in Europe and the USA. In 1994 and 1995 (snapshot data), databases of annual review returns recorded the ICS use as 36% in the UK (Koch 1997), and 26% in North America (1995 snapshot data) (Konstan 1999). Clinicians at CF centres treating children reported prescribing them to a median of 44% of children (Balfour-Lynn 1999). Data from 2001 entries showed that in the UK (CF Trust Database) 52% children and 55% adults were prescribed ICS, whilst in the USA they were given to 41% children and 48% adults (Epidemiologic Study of CF). Whilst more recent data from UK CF Trust Registry shows that in 2007, 21% children under 16 years and 23% adults were prescribed regular ICS; and North American data from the CFF registry showed that in 2005, 46% patients received ICS (Balfour-Lynn 2008).

The use of ICS may be justified as a form of symptomatic prophylaxis for those with recurrent wheezing or CF asthma (Balfour-Lynn 2002), but they are also prescribed by many clinicians purely for their perceived benefit as an anti-inflammatory agent. It is therefore important to establish whether this practice is beneficial overall for people with CF or whether their potential for harm overrides any benefit.

This version of the review is an update of previously published versions (Balfour-Lynn 2000; Balfour-Lynn 2009; Balfour-Lynn 2012; Balfour-Lynn 2014; Balfour-Lynn 2016). Due to the lack of research in this area, we do not envisage undertaking any further updates.

Inhaled corticosteroids for cystic fibrosis (Review)

OBJECTIVES

The objective of this review was to assess the effectiveness of regular use of ICS when compared to not receiving ICS, in the management of people with CF. We assessed whether ICS:

1. improve lung function (including tests of lung function, bronchial hyperreactivity, exercise tolerance);
2. reduce the need for hospital admission or antibiotic treatment for respiratory exacerbations;
3. improve the well-being of people with CF (in relation to nutritional status and quality of life);
4. improve survival;
5. are associated with harmful effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs (using allocation methods such as alternate allocation to treatment and control group) were included.

Types of participants

People with CF who had been diagnosed by clinical criteria and sweat or genetic testing, or both, regardless of age or clinical severity.

Types of interventions

Any ICS administered using any inhalation device (including metered-dose inhalers, dry powder inhalers, spacer devices and nebulisers) for a period of not less than two weeks, compared to either placebo or standard treatment.

Types of outcome measures

Primary outcomes

1. Objective measures of lung function
 - a. absolute values and change (L and % predicted) of forced expiratory volume in one second (FEV₁)
 - b. absolute values and change (L and % predicted) of the forced vital capacity (FVC)

Secondary outcomes

1. Changes in bronchial hyperreactivity as measured by challenge with a bronchoconstricting agent such as histamine, methacholine or cold air
2. Improvement in exercise tolerance (objective or subjective)
3. Respiratory exacerbations (post hoc restructuring change)
 - a. number of exacerbations
 - b. number of days in hospital for respiratory exacerbations
 - c. number of days on intravenous antibiotics for respiratory exacerbations
 - d. time to next exacerbation
4. Change in nutritional indices
 - a. change in height centile
 - b. change in weight centile

- c. change in body mass index (BMI) or % predicted weight for height
- d. changes in growth velocity (change in cm per treatment interval)
- e. other
5. Quality of life and symptom scores (post hoc change)
6. Adverse effects
 - a. local effects (e.g. oral candida infections (diagnosed clinically or microbiologically), hoarseness)
 - b. systemic effects (e.g. skin changes, diabetes mellitus, osteoporosis, Cushingoid appearance, cataract, mild or severe opportunistic infection, adrenal insufficiency (post hoc addition))
7. Survival (assessed at 6 months, 12 months and annually thereafter)

Search methods for identification of studies

Trials are eligible for inclusion irrespective of publication status (e.g. abstract or online trial report) or language.

Electronic searches

Relevant trials were identified from the Group's Cystic Fibrosis Trials Register using the terms: anti-inflammatory AND steroid AND (inhaled or unknown).

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's [website](#).

Date of the most recent search of the Group's Trials Register: 19 November 2018.

We also searched the following trials registries on 04 December 2018 ([Appendix 1](#)):

- the World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch);
- ClinicalTrials.gov (www.clinicaltrials.gov).

Searching other resources

We additionally searched the reference lists of all trials identified. We contacted two pharmaceutical companies manufacturing ICS preparations to identify unpublished trials; one of these did not identify any new trials and to date we have not received a reply from the second company. For a previous update, we wrote to lead authors of nine eligible trials, published only as abstracts or as full reports but with incomplete information for assessment of methodological quality or for reporting of outcomes. Replies were received from five and any information provided was incorporated.

Data collection and analysis

Selection of studies

For the update two authors (KW, IBL) independently selected trials to be included in the review. There was no disagreement between the authors as to which trials to include.

Data extraction and management

To ensure consistency, each author independently extracted data using a standard data extraction form (for each trial two of the three listed authors did this). They assessed the outcome measures listed above in the short term (between 2 and 12 weeks), the medium term (between 3 and 12 months) and long term (over 12 months).

The WISE trial is a withdrawal trial and all participants had been on steroids for a number of years before these were withdrawn. The other trials present data from the start of treatment with steroids. The review authors decided that the data from the withdrawal trial should be presented on a different graph to the data from the other trials, since the populations in the placebo arms of the trials are heterogeneous and that there may possibly be carry-over effect which will tend to reduce the difference.

Assessment of risk of bias in included studies

For the 2019 update, two authors (KW, SS) independently assessed risk of bias using the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). As per the domains below, they assigned concealment of allocation and method used to generate the random sequence to one of three categories: adequate, unclear or inadequate which related to a low, unclear or high risk of bias respectively. They defined the reported intention-to-treat analysis as complete, when less than 15% of participants were excluded, or incomplete when more than 15% were excluded from the final analysis; the risk of bias increased as the number of participants excluded from the final analysis increased. They recorded the reporting of double blinding as either present or absent; they considered the absence of blinding to lead to a high risk of bias.

Review authors resolved minor differences between the two authors in determining adequacy of random sequence generation in one trial and concealment of allocation in two trials by discussion, as were differences in assessing the completeness of intention-to-treat analysis in two trials. Assessments were otherwise concordant. For a previous update, review authors contacted trial investigators for clarification on methodological issues, including randomisation method and steps undertaken to ensure concealment of allocation. Authors have taken relevant information received into account.

Sequence generation

'Yes', if the investigators generated the allocation sequence using techniques such as a random-number table; a computer random-number generator; coin tossing; shuffling cards or envelopes; throwing dice.

'No', if the investigators generated the allocation sequence using techniques such as odd or even date of birth; date (or day) of admission; hospital or clinic record number.

'Unclear', if there was insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.

Allocation concealment

'Yes', if the investigators concealed the allocation sequence using methods such as central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.

'No', if the participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on; using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number.

'Unclear', if there was insufficient information to permit judgement of 'Yes' or 'No'. This was usually the case if the investigators did not describe the method of concealment at all or not in sufficient detail to allow a definite judgement, for example if the investigators described the use of assignment envelopes, but it remained unclear whether envelopes were sequentially numbered, opaque and sealed.

Blinding

'Yes', if there was no blinding, but the review authors judged that the outcome and the outcome measurement was not likely to be influenced by lack of blinding; blinding of participants and key trial personnel was ensured, and unlikely that the blinding could have been broken; either participants or some key trial personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

'No', if there was no blinding or incomplete blinding, and the outcome or outcome measurement was likely to be influenced by lack of blinding; investigators attempted the blinding of key trial participants and personnel, but likely that the blinding could have been broken; either participants or some key trial personnel were not blinded, and the non-blinding of others was likely to introduce bias.

'Unclear', if there was insufficient information to permit judgement of 'Yes' or 'No' or the trial did not address this outcome.

Incomplete data assessment

'Yes', if there were no missing outcome data; reasons for missing outcome data were unlikely to be related to true outcome; missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; missing data were imputed using appropriate methods.

'No', if the reasons for missing outcome data were likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for

dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes was enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

'Unclear', if there was insufficient reporting of attrition or exclusions to permit judgement of 'Yes' or 'No' (e.g. numbers randomised were not stated, no reasons for missing data were provided); the trial did not address this outcome.

Selective outcome reporting

'Yes', if the trial protocol was available and the investigators reported all of the pre-specified (primary and secondary) outcomes that were of interest in the review in the pre-specified way; the trial protocol was not available, but it was clear that the published reports included all expected outcomes, including those that were pre-specified.

'No', if not all of the trial's pre-specified primary outcomes were reported; one or more primary outcomes was reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that they could not be entered in a meta-analysis; the trial report failed to include results for a key outcome that would be expected to have been reported for such a trial.

'Unclear', if there was insufficient information to permit judgement of 'Yes' or 'No'.

Other sources of bias

'Yes', if the trial appeared to be free of other sources of bias.

'No', if there was at least one important risk of bias. For example, the trial had a potential source of bias related to the specific trial design used; or stopped early due to some data-dependent process (including a formal-stopping rule); or had extreme baseline imbalance; or has been claimed to have been fraudulent; or had some other problem.

'Unclear', if there was either: insufficient information to assess whether an important risk of bias existed; or insufficient rationale or evidence that an identified problem would introduce bias.

Measures of treatment effect

The statistical analysis proposed, included calculation of a pooled estimate of treatment effect for each dichotomous outcome across all trials (odds of outcome in participants allocated to receive treatment compared with odds of outcome in participants allocated to control group); and calculation of a pooled estimate of treatment effect for each continuous outcome across all trials in the form of a mean difference (MD). For continuous variables, the authors recorded mean absolute change from baseline for each group, or mean post-treatment values and standard deviation (SD) for each group.

Unit of analysis issues

Elbourne discusses methods for meta-analysing cross-over trials (Elbourne 2002). The methods discussed rely on the data that are reported within the primary paper. The method that has been adopted within this review uses data from the first period only, ignoring the second-period data. If results of the first period only were not available, the results of the trial were described in the text.

Dealing with missing data

In order to allow an intention-to-treat analysis, the authors sought data on the number of participants with each outcome event listed above, by allocated treatment group, irrespective of whether the participant complied with treatment or was later excluded from treatment or follow-up.

The authors also contacted the trial investigators for clarification of information in their publications or additional data where necessary.

Assessment of heterogeneity

If indicated, the authors examined heterogeneity between trial results using a standard χ^2 test. The authors also assessed the degree of heterogeneity between trials using the I^2 statistic (Higgins 2003). This measure describes the percentage of total variation across trials that are due to heterogeneity rather than by chance; the values of I^2 lie between 0% and 100%, and can be simply categorized so that heterogeneity is low when I^2 has a value of 25%, moderate if I^2 has a value of 50%, and high when I^2 has a value of 75% (Higgins 2003).

Assessment of reporting biases

Reports of all the included trials were checked to see that all the stated outcomes were reported and the results are presented in the 'Risk of bias table' in [Characteristics of included studies](#)

Data synthesis

The authors have analysed the data using a fixed-effect model. If in future, they are able to combine data and establish a moderate or high degree of heterogeneity between trials, they will analyse the combined data using a random-effects model.

Subgroup analysis and investigation of heterogeneity

If in future, the authors are able to include and combine a sufficient number of trials and they identify at least moderate heterogeneity (as defined above), the authors plan to investigate this by undertaking subgroup analyses comparing age, atopy with non-atopy, baseline lung function and individuals infected with *Pseudomonas aeruginosa* with those not infected with *P. aeruginosa*. It is unlikely, however, that this will be possible.

Sensitivity analysis

If appropriate, the authors planned to undertake a sensitivity analysis by allocation method (quasi-RCT versus RCT).

Summary of findings tables

We prepared a summary of findings tables for each comparison included in the review. We listed population, setting, intervention and comparison and reported an illustrative risk for the experimental and control intervention where it was possible to

do that from the available data ([Schünemann 2011](#)). We graded the overall quality of the body of evidence as high, moderate, low or very low using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) ([Schünemann 2006](#)). We based our judgements on the risk of bias within the trials, their relevance to our population of interest (indirectness), unexplained heterogeneity or inconsistency, imprecision of the results or high risk of publication bias. We downgraded the evidence once if the risk was serious and twice if the risk was deemed to be very serious for each domain and described the rationale for each judgement in footnotes to the table.

For each comparison we reported the following outcomes:

- change in FEV₁ % predicted;
- change in FVC % predicted;
- improvement in bronchial hyperreactivity;
- improvement in exercise tolerance;
- days in hospital for respiratory exacerbation;
- quality of life; and

- adverse effects.

RESULTS

Description of studies

Results of the search

The searches identified 35 citations, of which 27 referred to 13 trials meeting the inclusion criteria for this review ([Austrian Trial 1995](#); [Belgian Trial 2007](#); [Canadian Trial 1997](#); [CF WISE 2006](#); [Danish Trial 1983](#); [Danish Trial 1997](#); [Dutch Trial 1995](#); [German Trial 1999](#); [Irish Trial 1995](#); [Swiss Trial 1996](#); [Turkish Trial 2017](#); [UK Trial 1996](#); [UK Trial 1997](#)).

Seven citations referred to four trials which were excluded ([Australia Trial 2000](#); [Bessaci 2008](#); [USA Trial 1996](#); [USA Trial 1998](#)). The final citation referred to a trial which is currently listed in [Studies awaiting classification](#) until the methods of the trial can be clarified with the investigators ([Kapustina 2008](#)).

This information is presented in a flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram.

Included studies

Full reports have been published for both Danish trials ([Danish Trial 1983](#); [Danish Trial 1997](#)), the Dutch and Swiss trials ([Dutch Trial](#)

[1995](#); [Swiss Trial 1996](#)), two UK trials ([CF WISE 2006](#); [UK Trial 1997](#)), the German trial ([German Trial 1999](#)), the Belgian trial ([Belgian Trial 2007](#)) and the Turkish trial ([Turkish Trial 2017](#)). There are four trials

reported as abstracts or conference proceedings only (Austrian Trial 1995; Canadian Trial 1997; Irish Trial 1995; UK Trial 1996).

Trial Design

There were 10 parallel-designed trials (Austrian Trial 1995; Belgian Trial 2007; Canadian Trial 1997; CF WISE 2006; Danish Trial 1983; Danish Trial 1997; German Trial 1999; Swiss Trial 1996; Turkish Trial 2017; UK Trial 1996) and three were cross-over in design (Dutch Trial 1995; Irish Trial 1995; UK Trial 1997). One trial was a withdrawal trial in which participants who were already taking inhaled fluticasone were randomised to continue fluticasone or start placebo (CF WISE 2006). All trials were placebo-controlled, with the exception of two (German Trial 1999; Swiss Trial 1996).

Two trials were multicentre (Belgian Trial 2007; CF WISE 2006) and 11 trials were based in a single centre (Austrian Trial 1995; Canadian Trial 1997; Danish Trial 1983; Danish Trial 1997; Dutch Trial 1995; German Trial 1999; Irish Trial 1995; Swiss Trial 1996; Turkish Trial 2017; UK Trial 1996; UK Trial 1997). The trials randomised between 7 and 171 participants per trial; collectively they randomised 525 participants. Gender distribution was reported in 10 trials, which stated that 49.6% (206 out of 415) of participants randomised were male.

Participants

Four trials were specifically in children (Belgian Trial 2007; Canadian Trial 1997; Turkish Trial 2017; UK Trial 1997), four trials included both children and adults (CF WISE 2006; Danish Trial 1983; Danish Trial 1997; Swiss Trial 1996) and four enrolled only adults (Dutch Trial 1995; German Trial 1999; Irish Trial 1995; UK Trial 1996). In the remaining trial it was not explicitly stated whether children or adults or both were enrolled, although it was conducted in a paediatric department (Austrian Trial 1995).

Participant eligibility was based on clinical diagnosis of CF, usually with confirmation by sweat test. Two trials reported genotype distribution (CF WISE 2006; UK Trial 1997). Eligibility according to severity of pulmonary involvement varied between the trials. Acute pulmonary exacerbation was an entry criterion in the Austrian trial (Austrian Trial 1995); chronic *P aeruginosa* lung infection in both Danish trials (Danish Trial 1983; Danish Trial 1997); moderate to severe bronchial obstruction (FEV₁ less than 55% predicted) in the Swiss trial (Swiss Trial 1996); 'mild disease' (mean FEV₁ 85% predicted) in the Irish trial (Irish Trial 1995); 'established pulmonary disease' in the 1996 UK trial (UK Trial 1996); and 'stable' disease in the German trial (German Trial 1999). In the Belgian trial participants had mild to moderate lung disease and FEV₁ had to be at least 60% predicted (Belgian Trial 2007). In the withdrawal trial, FEV₁ had to be greater than or equal to 40% predicted and participants had to have been taking ICS for more than three months (CF WISE 2006). Where exclusion criteria were stated, these generally included recent treatment with oral or ICS and allergic bronchopulmonary aspergillosis. Two trials excluded people with asthma but not those with atopy (Danish Trial 1997; UK Trial 1997).

Interventions

Beclomethasone was given for periods of between 4 and 22 weeks in four trials (Austrian Trial 1995; Danish Trial 1983; Irish Trial 1995; Swiss Trial 1996); budesonide for six weeks, eight weeks and six months in three trials (Danish Trial 1997; Dutch Trial 1995; Turkish Trial 2017); and fluticasone for periods of between three weeks and

two years in four trials (Belgian Trial 2007; Canadian Trial 1997; German Trial 1999; UK Trial 1996).

In four trials, the active treatment was inhaled beclomethasone, given via metered dose inhaler with or without a spacer device (Austrian Trial 1995; Danish Trial 1983; Irish Trial 1995; Swiss Trial 1996). The daily dosage schedule was 1500 mcg except in the Danish trial, where it was 400 mcg (Danish Trial 1983). The duration of active treatment assessed ranged from 4 to 22 weeks.

In three trials, the active treatment was budesonide, total daily dose 1600 mcg given as dry powder for six months (Danish Trial 1997), by metered dose inhaler for six weeks (Dutch Trial 1995) or 2 mg by nebuliser (Turkish Trial 2017).

In the remaining trials, the active intervention was fluticasone propionate given as 1000 mcg daily by metered dose inhaler with a spacer device for 22 days (German Trial 1999) or for one year (Belgian Trial 2007; Canadian Trial 1997) or for two years (UK Trial 1996) or as 800 mcg daily as a dry powder for six weeks (UK Trial 1997).

In the withdrawal trial there was a two-month period in which participants either continued to take fluticasone propionate via a spacer device or were switched to an equivalent dose of fluticasone propionate if they were already taking budesonide or beclomethasone dipropionate (CF WISE 2006). After the two-month period they were then randomised to continue taking fluticasone propionate or start a placebo.

All treatment was given on an outpatient basis, except for the Swiss trial (Swiss Trial 1996).

Outcomes

Lung function measurements were a specified outcome in 12 trials, but were not reported in two trials (Canadian Trial 1997; Irish Trial 1995). Following communication with the authors of the Canadian trial, data on FEV₁ have been provided, but these were not analysable in the review (Canadian Trial 1997). In 11 of the trials both FEV₁ and FVC were reported, with the remaining trial measuring peak flow rate rather than FEV₁ (Danish Trial 1983).

Nine trials reported absolute values for lung function at a number of time-points (Belgian Trial 2007; CF WISE 2006; Danish Trial 1983; Dutch Trial 1995; German Trial 1999; Swiss Trial 1996; Turkish Trial 2017; UK Trial 1996; UK Trial 1997). Two of these trials measured lung function in L (Dutch Trial 1995; UK Trial 1996). The Dutch cross-over trial reported the mean absolute FEV₁ and FVC in L for each treatment period, but did not provide SDs (Dutch Trial 1995); and the 1996 UK trial reported FEV₁ and FVC as absolute mean (SD) value in L at baseline, 6 months and 24 months (UK Trial 1996). Seven trials reported lung function as % predicted (Belgian Trial 2007; CF WISE 2006; Danish Trial 1983; German Trial 1999; Swiss Trial 1996; Turkish Trial 2017; UK Trial 1997). In the Belgian trial, the mean % predicted FEV₁ and FVC were reported at baseline, 6 and 12 months pre- and 20 minutes post-salbutamol (bronchodilator) as a measure of bronchial lability (Belgian Trial 2007). The CF-WISE trial reported the mean % predicted FEV₁ and FVC at baseline, two, four and six months (CF WISE 2006). The German trial reported lung function as median (SD) % predicted at baseline and after 21 days treatment (German Trial 1999). The Turkish trial reported mean (SD)

FEV₁ and FVC % predicted before and after eight weeks of treatment (Turkish Trial 2017). Finally, the 1997 UK cross-over trial reported the mean % predicted FEV₁ and FVC with 95% confidence intervals (CI) for each treatment period and after further communication with the investigators, SDs were also provided (UK Trial 1997).

Four trials reported the change in lung function from baseline (Belgian Trial 2007; CF WISE 2006; Danish Trial 1997; Swiss Trial 1996). Only the 1997 Danish trial reported the change from baseline in L; data for the mean change were available at three and six months but no SDs were provided (Danish Trial 1997). Three trials reported the change from baseline in % predicted. The Belgian trial reported the mean (SD) change in % predicted FEV₁ and FVC post-salbutamol at 12 months (Belgian Trial 2007); the CF-WISE trial reported means and SDs at baseline, two, four and six months (CF WISE 2006); and the Swiss trial reported the mean change in FEV₁ and FVC % predicted but without SDs (Swiss Trial 1996).

Bronchial reactivity was assessed in four trials: by histamine challenge alone (Dutch Trial 1995); histamine challenge or exercise test (Danish Trial 1997); or by methacholine challenge (Irish Trial 1995, Turkish Trial 2017). In the Dutch cross-over trial, results were expressed as mean log PC20 and as geometric mean PC20 at baseline and after budesonide, but no data were reported for the placebo treatment period (Dutch Trial 1995). In the 1997 Danish trial, data were expressed as mean change in histamine dose steps from baseline within each group, but without SDs, and as mean difference in mean change in histamine dose steps with 95% CI between groups (Danish Trial 1997). The Turkish trial reported bronchial hyperreactivity (BHR) where BHR was defined as a PC20 of 8 mg/mL or lower (Turkish Trial 2017). Data were not reported in the Irish trial (Irish Trial 1995).

Hospital admissions and antibiotic usage were specified as outcomes in the Dutch trial, but no data were reported (Dutch Trial 1995). Overall antibiotic usage was reported in the 1996 UK trial, but not by treatment group (UK Trial 1996). Data regarding days in hospital and days on antibiotics were provided for a previous review update by the Canadian investigators (Canadian Trial 1997). In the CF-WISE withdrawal trial, the primary outcome reported was the time to first respiratory exacerbation. Secondary outcomes reported were the number of participants who had unplanned courses of oral or intravenous antibiotics and the median number of courses required per participant. The number of individuals requiring rescue bronchodilator and the median number of doses per participant were also reported (CF WISE 2006). The de Boeck trial reported the mean number of respiratory exacerbations between groups and reported Brasfield chest X-ray scores (median and quartiles) at baseline, 6 and 12 months (Belgian Trial 2007).

Symptoms were specified as outcomes in four trials (Dutch Trial 1995; German Trial 1999; UK Trial 1996; UK Trial 1997). The incidence of *P aeruginosa* positive respiratory cultures were recorded in two trials (Belgian Trial 2007; CF WISE 2006).

Clinical status and nutritional indices were specified as outcomes in the Canadian trial but have not been reported to date (Canadian Trial 1997). In the Belgian trial, the change in longitudinal growth (height) was recorded at baseline then at three-monthly intervals during the treatment duration of one year and then for a further one

year after discontinuation (and for up to two years in a subgroup of participants) (Belgian Trial 2007). In the CF-WISE withdrawal trial, height was measured at the start and end of the trial in the paediatric participants and the review authors were provided with these data (CF WISE 2006). The UK trial assessed well-being and appetite using a visual analogue scale (UK Trial 1997); but formal measurement of quality of life was not attempted in any trial.

The number of deaths was reported in one trial (CF WISE 2006); but no other information on survival was reported in any other trial.

Specific adverse effects were recorded in five trials (Belgian Trial 2007; Canadian Trial 1997; CF WISE 2006; Danish Trial 1997; UK Trial 1997). In two trials, adverse effects were reported as not differing significantly or not occurring, but no details were provided (Dutch Trial 1995; UK Trial 1996). In the remaining trials no comment about adverse effects was made.

Outcomes not listed in the review which were reported by trials included sputum or serum markers of inflammation which were measured in six trials (Austrian Trial 1995; Danish Trial 1983; German Trial 1999; Irish Trial 1995; Turkish Trial 2017; UK Trial 1997); serum IgG and HbA1C were recorded at baseline, 6 and 12 months in one trial (Belgian Trial 2007) and oxidative status as measured by plasma malondialdehyde in one trial (Turkish Trial 2017). Also, adherence to treatment was monitored and reported in the two trials using fluticasone delivered by Diskhalers (Danish Trial 1997; UK Trial 1997).

Excluded studies

Four trials (seven citations) were excluded (Australia Trial 2000; Bessaci 2008; USA Trial 1996; USA Trial 1998). Published details for the Australian trial were insufficient to determine whether treatments were allocated by random or quasi-random methods and further details could not be obtained from the authors; therefore, this trial was excluded (Australia Trial 2000). Two references identified relate to a trial of seretide (which contains an inhaled steroid) plus salmeterol which is not a steroid; since this trial does not consider an ICS alone, it can not be included (Bessaci 2008). Two citations referring to one trial from the USA were identified, but this trial was deemed ineligible, as the outcomes reported were not specified as outcomes for this review (USA Trial 1998). A further two citations related to an observational study from the USA which did not meet the inclusion criteria as treatment had not been allocated on a random basis (USA Trial 1996).

Studies awaiting assessment

We have listed one trial as awaiting assessment as it is unclear whether it was randomised and if so how (Kapustina 2008). Investigators divided 40 children with CF (23 females and 17 males) aged 5 to 17.4 years and all with "severe" phenotype, into two groups. The 14 children in Group 1 inhaled corticosteroids for between 6 and 120 months and the 26 children in Group 2 were given oral steroids for between 1 month and 185 months. The primary outcome measured was bone mineral density in the lumbar spine.

Risk of bias in included studies

Risk of bias judgements are summarised in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Austrian Trial 1995	?	?	+	?	?	?
Belgian Trial 2007	+	?	+	+	+	+
Canadian Trial 1997	?	+	+	+	-	?
CF WISE 2006	+	+	+	+	+	+
Danish Trial 1983	?	?	+	+	+	+
Danish Trial 1997	?	+	+	+	+	+
Dutch Trial 1995	?	+	+	?	-	?
German Trial 1999	+	-	-	?	+	+
Irish Trial 1995	?	+	+	+	+	?
Swiss Trial 1996	?	?	-	?	+	+
Turkish Trial 2017	+	?	-	+	+	+
UK Trial 1996	?	?	+	+	+	?
UK Trial 1997	?	+	+	+	+	?

Allocation

The method used to generate the random sequence was clearly described in four trials, which we judged to have a low risk of bias: the German trial, which used a random number row to determine the intervention for the first participant, and then used alternation to determine the groups for the remaining participants ([German Trial 1999](#)); the CF WISE trial, which used randomisation by permuted blocks of four ([CF WISE 2006](#)); the Belgian trial, which used random numbers ([Belgian Trial 2007](#)); and the Turkish trial which used a random number row and participants with odd and even numbers were randomised to receive budesonide or placebo ([Turkish Trial 2017](#)). The method of randomisation in the remaining trials is unclear and not stated in the trial reports. These other trials therefore have an unclear risk of bias.

The concealment of allocation was deemed to be adequate in six trials, which therefore had a low risk of bias: in one trial it was stated that treatment codes were not broken before a clean file was declared by the data manager ([Danish Trial 1997](#)); in the Dutch trial treatment and placebo were given by blinded metered-dose inhalers supplied by the pharmaceutical company ([Dutch Trial 1995](#)); and in the CF WISE trial allocation was carried out independently over the telephone from the Clinical Trials and Evaluation Unit of the Royal Brompton Hospital to the trial centre ([CF WISE 2006](#)). Trialists supplied information from three trials where sealed envelopes were used, therefore the risk of bias in these trials was low ([Canadian Trial 1997](#); [Irish Trial 1995](#); [UK Trial 1997](#)). Concealment of allocation was deemed to be inadequate in the German trial which used a method of alternation allowing the trial investigators to foresee to which group the next participant would be assigned; this trial was judged to have a high risk of bias ([German Trial 1999](#)). The remaining trials did not discuss allocation concealment and were judged to have an unclear risk of bias.

Blinding

Nine trials were described as double-blind and judged to have a low risk of bias ([Austrian Trial 1995](#); [Belgian Trial 2007](#); [Canadian Trial 1997](#); [CF WISE 2006](#); [Danish Trial 1983](#); [Danish Trial 1997](#); [Dutch Trial 1995](#); [Irish Trial 1995](#); [UK Trial 1997](#)). In three trials there was a high risk of bias; one trial was only single blinded due to the intervention and placebo not being dispensed in similar vials ([Turkish Trial 2017](#)). Similarly, in one trial interventions were given either twice or three times daily (no placebo) ([Swiss Trial 1996](#)) and the final trial was described as open label ([German Trial 1999](#)).

Further details are listed in the 'Risk of bias tables' section of the [Characteristics of included studies](#).

Incomplete outcome data

Eight trials were judged to have a low risk of bias. In three trials an intention-to-treat analysis was based on all participants ([CF WISE 2006](#); [Danish Trial 1997](#); [Irish Trial 1995](#)). In two trials less than 15% of participants were excluded ([Belgian Trial 2007](#); [UK Trial 1997](#)). In two trials more than 15% of participants were excluded, but reasons were given for their exclusion and the numbers were equal across groups; reasons for exclusion included clinical deterioration, failure to take treatment or failure to attend for the follow-up assessments ([Danish Trial 1983](#); [UK Trial 1996](#)). The Turkish trial did not use an intention-to-treat analysis and only analysed the participants that completed the trial, but less than 15% were excluded and so we deemed it to be at low risk of bias ([Turkish Trial](#)

[2017](#)). In the remainder of the trials judgements could not be made from the information available, and these were judged to have an unclear risk of bias.

Selective reporting

We examined the published papers and identified the following instances of selective reporting in three trials, which could be a potential source of bias ([Canadian Trial 1997](#); [Dutch Trial 1995](#); [UK Trial 1996](#)). Clinical status and nutritional indices were specified as outcomes in the Canadian trial but have not been reported to date ([Canadian Trial 1997](#)). Hospital admissions and antibiotic usage were specified as outcomes in the Dutch trial, but no data were reported ([Dutch Trial 1995](#)). In the 1996 UK trial, FVC was recorded, but not reported, and although participants kept a symptom diary card, data were not reported from this either ([UK Trial 1996](#)).

Other potential sources of bias

The Canadian trial was halted prematurely making it difficult to draw any conclusions ([Canadian Trial 1997](#)). Four trials have never been published in peer-reviewed journals ([Austrian Trial 1995](#); [Canadian Trial 1997](#); [Irish Trial 1995](#); [UK Trial 1996](#)). The Dutch trial was of cross-over design, but did not describe any washout period; we have judged this trial to have an unclear risk of bias.

Effects of interventions

See: [Summary of findings 1 Summary of findings: inhaled corticosteroids compared with placebo for cystic fibrosis](#)

We were unable to undertake pooled analyses of any treatment outcome partly because reports differed in the way data were summarised and partly because some data needed for the analysis, for example SDs or standard errors (SEs), were not available from the published reports. As stated above, data from the CF WISE trial are presented, but results from this trial were not pooled with other trials because the trial was a withdrawal trial ([CF WISE 2006](#)). There were also differences between trials in the outcomes reported, so that for some variables, only a single trial result could be reported. The results are presented by outcome in the order in which they appear in the aims of the review. Within each outcome, data are discussed separately for parallel and cross-over trials but sequenced by short-, medium- and long-term outcomes as specified above ([Methods](#)).

The effects of interventions are summarised in the summary of findings table, the quality of the evidence has been graded for pre-defined outcomes (see above) and definitions of these gradings provided ([Summary of findings 1](#)).

Primary outcome

1. Objective measures of lung function

a. FEV₁

There were 12 trials which measured FEV₁ ([Belgian Trial 2007](#); [Canadian Trial 1997](#); [CF WISE 2006](#); [Danish Trial 1983](#); [Danish Trial 1997](#); [Dutch Trial 1995](#); [German Trial 1999](#); [Irish Trial 1995](#); [Swiss Trial 1996](#); [Turkish Trial 2017](#); [UK Trial 1996](#); [UK Trial 1997](#)). Following communication with the authors of the Canadian trial, data have been provided which showed no significant difference at baseline in FEV₁ ([Canadian Trial 1997](#)). Illustrations were also provided which the authors interpreted as showing that lung

function did not alter through the trial in either group over a nine-month period. However, no actual data were available beyond baseline ([Canadian Trial 1997](#)).

Absolute values (L)

Two trials (52 participants) reported data for absolute FEV₁ (L) ([Dutch Trial 1995](#); [UK Trial 1996](#)), but we were only able to analyse the data from the 1996 UK trial ([UK Trial 1996](#)); after six months of fluticasone or placebo, mean absolute FEV₁ tended to be higher in the treatment (n = 18) than in the placebo group (n = 15), but this was not statistically significant, mean difference (MD) 0.16 L (95% CI -0.27 to 0.59) ([Analysis 1.1](#)). Three participants in the placebo group were not included in this analysis (less than 15% exclusions). After 24 months of treatment, again no significant differences between groups were observed, but this analysis was based on less than half (n = 17) of the 36 participants originally randomised, MD 0.24 L (95% CI -0.34 to 0.82) ([Analysis 1.1](#)). In the Dutch cross-over trial, mean FEV₁ (L) was reported as similar at the end of both six-week treatment periods, being 2.3 L after budesonide and 2.2 L after placebo ([Dutch Trial 1995](#)). These data were based on 12 of the original 16 participants randomised; further data (including SDs) are not available from the authors.

Absolute values (% predicted)

Six trials (328 participants) reported on absolute values for FEV₁ % predicted ([Belgian Trial 2007](#); [CF WISE 2006](#); [German Trial 1999](#); [Swiss Trial 1996](#); [Turkish Trial 2017](#); [UK Trial 1997](#)); and we were able to present data in a forest plot for four of these ([Belgian Trial 2007](#); [CF WISE 2006](#); [Swiss Trial 1996](#); [Turkish Trial 2017](#)). In the Belgian trial, there was no difference in the mean % predicted FEV₁ at either 6 or 12 months either pre- or 20 minutes post-salbutamol. No significant difference was seen between ICS and placebo in either the Swiss trial or the Turkish trial ([Analysis 1.2](#)). The CF-WISE trial results are presented separately as this was a withdrawal trial. They reported no difference in the mean % predicted FEV₁ at two months, four months or six months ([CF WISE 2006](#)), MD 3.00% predicted (95% CI -2.55 to 8.55) ([Analysis 1.3](#)).

The German trial reported median (SD) FEV₁ % predicted and so could not be included in the analysis. No improvement in FEV₁ % predicted was shown after therapy with fluticasone. The value at day 22 compared with baseline was not significantly different in either the fluticasone or placebo group (fluticasone (median (SD)): 53.2% (22.9%) versus 55.8% (21.6%), P > 0.1; placebo group: 56.3% (20.3%) versus 56.7% (25.8%), P > 0.2) ([German Trial 1999](#)). The data from the 1997 UK cross-over trial are not entered into the [Data and analyses](#) tables as first-period data could not be extracted ([UK Trial 1997](#)). The mean (SD) FEV₁ % predicted was similar at the end of both six-week treatment periods, being 66% (16.7%) after fluticasone and 67% (23.0%) after placebo, with 95% CI for the difference reported as -8% to 4%; these data were based on 22 of 23 participants originally randomised ([UK Trial 1997](#)).

Change from baseline (L)

Only the 1997 Danish trial (55 participants) reported the mean change from baseline in FEV₁ (L) at three and six months, but no SDs were provided ([Danish Trial 1997](#)). The change from baseline to the end of the trial was 0.002 L in the budesonide group compared to -0.098 L in the placebo group, but this was not significant (P > 0.1).

Change from baseline (% predicted)

The change from baseline in % predicted FEV₁ was recorded at different time points in three trials (250 participants) ([Belgian Trial 2007](#); [CF WISE 2006](#); [Swiss Trial 1996](#)). The quality of evidence for the change from baseline in FEV₁ % predicted was deemed to be low ([Summary of findings 1](#)).

In the Belgian trial, the change from baseline at 12 months was not significantly different between ICS and placebo, MD -0.50% predicted (95% CI -10.92 to 9.92) ([Analysis 1.4](#)). In the CF WISE trial, there was also no significant difference found after six months between those participants who continued treatment (n = 84) and those who were withdrawn (n = 87), MD -0.60 (95% CI -4.60 to 3.40) ([Analysis 1.5](#)). Additionally, in this trial, no change in lung function was found in the fluticasone group in those switching from a different ICS (budesonide or beclomethasone) to fluticasone ([CF WISE 2006](#)). In the Swiss trial, where treatment was given for 30 days as an inpatient, there was an improvement at 30 days of 7.9% in FEV₁ % predicted in those given beclomethasone (n = 25) and an improvement of 7.9% in those not given the drug (n = 24). There was no significant difference between the groups (P > 0.05) ([Swiss Trial 1996](#)).

b. FVC

There were 12 trials which measured FVC ([Belgian Trial 2007](#); [Canadian Trial 1997](#); [CF WISE 2006](#); [Danish Trial 1983](#); [Danish Trial 1997](#); [Dutch Trial 1995](#); [German Trial 1999](#); [Irish Trial 1995](#); [Swiss Trial 1996](#); [Turkish Trial 2017](#); [UK Trial 1996](#); [UK Trial 1997](#))

Absolute values (L)

Two trials (52 participants) measured FVC (L) before and after treatment ([Dutch Trial 1995](#); [UK Trial 1996](#)), but the UK 1996 trial did not present any results for this outcome. In the Dutch cross-over trial, mean FVC (L) was reported as similar at the end of both six-week treatment periods, being 3.6 L after budesonide and 3.3 L after placebo ([Dutch Trial 1995](#)). These data were based on 12 of the original 16 participants randomised; further data (including SDs) are not available from the authors.

Absolute values (% predicted).

Seven trials (376 participants) reported absolute FVC % predicted ([Belgian Trial 2007](#); [CF WISE 2006](#); [Danish Trial 1983](#); [German Trial 1999](#); [Swiss Trial 1996](#); [Turkish Trial 2017](#); [UK Trial 1997](#)); we were able to include four of these in our analyses ([Belgian Trial 2007](#); [CF WISE 2006](#); [Swiss Trial 1996](#); [Turkish Trial 2017](#)). Our analyses showed no difference between ICS and placebo in FVC % predicted at 30 days ([Swiss Trial 1996](#)), at 8 weeks ([Turkish Trial 2017](#)), at 6 months ([Belgian Trial 2007](#)) or at 12 months ([Belgian Trial 2007](#)) ([Analysis 1.6](#)). The CF WISE Trial also showed no difference between groups at two, four or six months ([CF WISE 2006](#)) ([Analysis 1.7](#)).

The 1983 Danish trial reported the median (range) % predicted FVC using data from 13 of the originally randomised 24 matched pairs after 16 weeks of treatment; these were 91% (51% to 112%) in the beclomethasone group and 78% (46% to 116%) in the placebo group ([Danish Trial 1983](#)). This trial was based on randomisation within matched pairs, but this was not reflected in the analyses which compared group medians rather than within-pair differences ([Danish Trial 1983](#)).

The German trial reported only that the results for FVC reflected those of FEV₁ and so could not be included in the analysis. No improvement in lung function parameters was seen following therapy ($P > 0.2$) ([German Trial 1999](#)).

In the 1997 UK cross-over trial, mean (SD) FVC was 78.4% predicted (12.6) for the active treatment period and 77.4% (21.9) for the placebo treatment period; data for the end of trial and since first-period data could not be extracted, the results are not entered into the analysis ([UK Trial 1997](#)).

Both the Canadian trial and the Irish trial reported that they measured FVC, but no results were reported ([Canadian Trial 1997](#); [Irish Trial 1995](#)).

Change from baseline (L)

One trial (55 participants) measured the change from baseline in FVC (L) but only stated in the results that the data followed that of FEV₁ in that there was no significant difference between budesonide and placebo ([Danish Trial 1997](#)).

Change from baseline (% predicted)

Three trials (250 participants) recorded the change from baseline in FVC % predicted ([Belgian Trial 2007](#); [CF WISE 2006](#); [Swiss Trial 1996](#)). The quality of evidence for the change from baseline in FVC % predicted was graded as low due to risk of bias within some of the included trials and low participant numbers ([Summary of findings 1](#)).

In the Belgian trial there was no significant difference found in the change in % predicted FVC at 12 months, MD 3.50% predicted (95% CI -5.59 to 12.59) ([Analysis 1.8](#)). Likewise, the withdrawal trial reported no significant difference in the change in % predicted FVC after six months, MD -0.50% predicted (95% CI -4.15 to 3.15) ([Analysis 1.9](#)) ([CF WISE 2006](#)). In the Swiss trial, between-group differences in change in % predicted FVC after 30 days of treatment were reported by the authors as not statistically significant, being 9.9% for the beclomethasone group and 7.9% for the control group, but no SDs were given ([Swiss Trial 1996](#)).

Secondary outcomes

1. Changes in bronchial hyperreactivity

This outcome was reported by three trials (100 participants) and was measured by challenge with a bronchoconstricting agent such as histamine, methacholine or cold air ([Danish Trial 1997](#); [Dutch Trial 1995](#); [Turkish Trial 2017](#)). We judged the quality of the evidence for this outcome to be very low ([Summary of findings 1](#)).

In the 1997 Danish trial, histamine PC₂₀ was measured in 41 of the 55 recruited participants and reported to increase by significantly more dose steps in those on budesonide compared with those on placebo; the change in histamine dose steps was reported in the full published paper as MD 1.13% (95% CI 0.01% to 2.26%) ($P < 0.05$) ([Danish Trial 1997](#)). In the Dutch trial, analyses based on 12 participants showed significant increases in mean log PC₂₀ histamine and geometric mean PC₂₀ histamine in the budesonide treatment period, but no equivalent data or reports were given for the placebo period. The response to exercise was reported as unchanged ([Dutch Trial 1995](#)). Bronchial hyperreactivity was measured with methacholine challenge in the Turkish trial and

found to be unchanged between groups ($P = 0.7$) ([Turkish Trial 2017](#)).

2. Improvement in exercise tolerance (objective or subjective)

Only the Dutch trial (12 participants) reported on this outcome and we deemed the quality of evidence to be very low ([Summary of findings 1](#)). Investigators compared the budesonide group to the placebo group in terms of dyspnoea score; scores ranged from zero to three, with three being most severe. The mean score for dyspnoea at rest was 0.38 in the budesonide group and 0.54 for the placebo group ($P < 0.05$), but scores were not significantly different on exercise 0.98 and 0.97 for the budesonide and placebo groups, respectively ([Dutch Trial 1995](#)).

3. Respiratory exacerbations

a. time to next exacerbation

The CF WISE withdrawal trial reported no significant difference in the time until the first exacerbation between the participants who continued treatment and those who were withdrawn from fluticasone ([CF WISE 2006](#)).

b. number of exacerbations

No significant difference was found in the number of respiratory exacerbations between groups in the Belgian trial ([Belgian Trial 2007](#)).

c. number of days in hospital for respiratory exacerbations

One trial (17 participants) reported on this outcome ([Canadian Trial 1997](#)). There was no significant difference between the fluticasone group and placebo group in the number of days spent in hospital at the nine-month follow-up, MD -0.10 days (95% CI -12.51 days to 12.31 days) ([Analysis 1.10](#)).

d. number of days on intravenous antibiotic for respiratory exacerbations

Four trials (240 participants) measured on antibiotic use for respiratory exacerbations ([Canadian Trial 1997](#); [CF WISE 2006](#); [Dutch Trial 1995](#); [UK Trial 1996](#)). We graded the quality of the evidence as very low ([Summary of findings 1](#)).

In the Canadian trial, there was no significant difference in the number of days on antibiotics at the nine-month follow up ([Canadian Trial 1997](#)), MD -4.40 days (95% CI -50.44 to 41.64) ([Analysis 1.11](#)). Similarly, there was no difference in intravenous (or oral) antibiotic use between the two groups at six months in the CF WISE trial ([CF WISE 2006](#)). The Dutch trial was stopped early and data for this outcome were not presented ([Dutch Trial 1995](#)). Overall antibiotic use was reported in the UK 1996 trial, but not by treatment group ([UK Trial 1996](#)).

4. Change in nutritional indices

In the 1997 UK trial (23 participants), no significant change in appetite scores was reported between the two six-week treatment periods ([UK Trial 1997](#)).

d. change in growth velocity

The main outcome of the Belgian trial was the effect on long-term growth and height was measured at three-monthly intervals during the trial period of one year and then for a further follow-up year ([Belgian Trial 2007](#)). During the first 12 months, growth

in the ICS group was significantly less than in the placebo group, MD -1.53 cm (95% CI -2.37 cm to -0.69 cm). The authors reported that participants did not "catch up" height in the 12 months following fluticasone discontinuation and a difference in growth rate of 2.4 cm was reported between the two groups after 24 months. In a subgroup of these participants growth data taken two years after treatment discontinuation showed "persistent growth impairment". Investigators from the CF WISE trial provided height data to the review authors for paediatric participants (CF WISE 2006). There was no significant difference in height between the 42 fluticasone participants and the 38 placebo participants, for whom data was available over the eight months trial duration, MD 0.60 cm (95% CI -0.46 cm to 1.66 cm) (Analysis 1.13).

5. Quality of life and symptom scores

One trial looked at well-being scores (23 participants). The 1997 UK trial found no significant change in well-being scores between the two six-week treatment periods (UK Trial 1997).

Three trials measured symptom scores (75 participants) (Dutch Trial 1995; UK Trial 1996; UK Trial 1997). Although participants in the 1996 UK trial kept a symptom diary card, data were not reported (UK Trial 1996). In the 1997 UK trial, no significant change in respiratory symptom scores was reported between the two six-week treatment periods (UK Trial 1997). In the Dutch trial, a small but significant ($P < 0.05$) improvement in cough or dyspnoea after six weeks of treatment was reported by adults randomised to budesonide (Dutch Trial 1995).

We judged the quality of the evidence for this outcome to be low.

6. Adverse effects

Specific adverse effects were reported in three trials (249 participants) (CF WISE 2006; Danish Trial 1997; UK Trial 1997). We graded the quality of the evidence for adverse events to be low (Summary of findings 1).

In the CF WISE trial adverse effects were classified as follows (CF WISE 2006).

1. CF pulmonary symptoms - 118 fluticasone, 132 placebo
2. CF non-pulmonary symptoms - 4 fluticasone, 12 placebo
3. Symptoms not relating to CF - 13 fluticasone 17 placebo

The paper reported that fewer participants in the fluticasone group withdrew from the trial due to lung-related adverse events (9% compared to 15%) with a relative risk (RR) of 0.59 (95% CI 0.12 to 1.48). There was one drug-related case of oral candidiasis in a participant taking fluticasone. In addition, there was no significant increase in rescue bronchodilator use between the groups (CF WISE 2006).

The 1997 Danish trial reported 17 adverse events in the budesonide group compared with 13 in the placebo group overall (Danish Trial 1997). It is unclear whether the numbers reported relate to individuals or individual episodes, although from the data presented it would appear that these are episodes. The budesonide group attended more frequently for outpatient visits than the placebo group (174 and 146 respectively). Events were reported more often in the budesonide group than the placebo group: hoarseness of voice, six and three occasions respectively; and monilia (oral thrush), four and two occasions respectively.

Haemoptysis, pharyngitis and chest pain were not reported at all in the placebo group, but reported on two, three and one occasion respectively in the budesonide group. Before and at the end of the trial, 15 participants underwent an adrenal function test (adrenocorticotrophic hormone (ACTH) stimulation test). One participant in each group had an abnormal response, which was found before the trial but in both cases the response had normalized by the end of the trial. It was reported that the response to ACTH did not differ between groups before or after treatment.

In the 1997 UK trial, two potentially drug-related adverse episodes were reported. One child in the fluticasone group developed peeling of the fingers for three days (in reality it is unlikely this relates to ICS), and another coughed for five minutes on one occasion after inhaling fluticasone (given as dry powder) (UK Trial 1997).

In addition, the Canadian trial was halted prematurely because it was noted that six out of the 17 participants enrolled had become colonised with *P aeruginosa* for the first time (Canadian Trial 1997). When the code was broken, five of the six participants enrolled were from the active treatment group ($n = 9$) and one from the placebo group ($n = 8$). In addition one participant from the active group, previously negative for both *P aeruginosa* and *Burkholderia cepacia*, grew *B cepacia* for the first time. Subsequently, the authors identified 56 out of 133 participants attending this clinic who were being treated with inhaled steroids, of whom nine had become culture-positive for *P aeruginosa* between three months and three years after starting this treatment.

Related to this, the Belgian trial reported no increase in the isolation of *P aeruginosa* between the two groups of participants (Belgian Trial 2007).

7. Survival

The CF WISE trial reported that there were no deaths (CF WISE 2006); the remaining trials did not report this outcome.

DISCUSSION

Summary of main results

The effectiveness of long-term treatment with ICS is of clinical relevance in view of its widespread use in clinical practice in Europe and North America. However, the findings of this review suggest that evidence to support this practice is still lacking. The review identified 13 trials reporting the use of inhaled steroids in 506 people with CF aged between 6 years and 55 years.

Lung function was measured before and after treatment with ICS in 12 of the 13 included trials. The different measures and time periods used precluded us from including the results in a meta-analysis, but no significant difference was found for either FEV₁ or FVC in any of the trials. We deemed the quality of this evidence to be low. Changes in bronchial hyperreactivity were only reported in three trials and we judged the quality of the evidence to be very low due to risk of bias within the trials. The Danish trial did, however, show an improvement in histamine reactivity in the budesonide group compared to placebo (Danish Trial 1997). There was no significant difference in exercise tolerance reported (only one trial) but the data available were limited and the quality of the evidence was judged as very low (Dutch Trial 1995). One trial reported number of days in hospital due to pulmonary exacerbation but the trial

was halted prematurely and so we judged the quality of evidence to be very low ([Canadian Trial 1997](#)). There was no significant difference in well being scores between ICS and placebo but it was only reported in one trial and again, the quality of evidence was judged as very low ([UK Trial 1997](#)). Two further trials reported symptoms or symptom scores, one finding no difference between groups ([UK Trial 1997](#)) and the other finding a small but significant improvement in cough or dyspnoea after budesonide ([Dutch Trial 1995](#)).

Adverse effects were not consistently assessed, although in most trials total daily dose of ICS was at the threshold identified in a systematic review as being associated with adrenal suppression ([Lipworth 1999](#)). Hoarseness of voice and oral candida were reported to be increased in those taking ICS in one trial, but this observation requires confirmation. An important concern relates to the risk of acquisition of *P aeruginosa* infection in those treated with corticosteroids. Although one trial was halted prematurely out of this concern, the data available are not conclusive ([Canadian Trial 1997](#)). Growth in childhood is always a concern with long-term corticosteroid use, and this includes inhaled corticosteroids. The Belgian trial has shown that one year of high-dose fluticasone adversely affected growth which did not catch up in the subsequent year (and in a subgroup followed for two years) ([Belgian Trial 2007](#)). However, the large difference in growth could have been due in part to the age difference between groups, 9.0 years for the placebo group and 8.2 years for the fluticasone group which might lead to a greater effect of pubertal growth over 24 months in the older (placebo) group. This was the first trial to look at growth over a reasonably long period and has provided important evidence that ICS can do harm in children with CF.

The CF WISE trial is the largest trial of ICS in children and adults with CF ([CF WISE 2006](#)). This trial showed that during the first six months after stopping ICS therapy, there was no apparent impact (adverse or beneficial), on the onset of acute chest exacerbations, decline in lung function, antibiotic prescribing and rescue bronchodilator use. Replacing the ICS with placebo was found to be safe as there was no significant increase in lung-related adverse effects leading to withdrawal from the trial, nor an increased need for oral corticosteroids. Many individuals with CF who are on ICS may no longer need them, but caution is advised due to the non-significant increase in lung-related adverse effects seen in the placebo group.

This review has found little evidence from existing trials to support the practice of routinely prescribing inhaled steroids in CF. Specifically, we cannot conclude that inhaled steroids are beneficial but there is some evidence that at a high dose, they adversely effect growth. There is also some evidence that withdrawal of ICS in the majority of those already being treated with them is safe.

Overall completeness and applicability of evidence

Trials were heterogeneous with respect to inclusion criteria, specifically age, severity of pulmonary involvement, clinical diagnosis of asthma and chronic lung infection with *P aeruginosa*. Trials also differed in duration of treatment. Treatment effects were assessed for short periods only in the cross-over trials (six weeks), but for longer periods in the parallel trials. Only one parallel trial reported treatment given over a two-year period, but follow-up and reporting at this interval are incomplete. Spirometric indices of lung function were measured in most trials, but could not be combined

in this review due to incompletely reported or unavailable data, as well as to differences in methods used to summarise data. Although five of the nine investigators contacted following the first issue of this review have supplied further information, a pooled estimate of treatment effects for lung function outcomes has not proved possible. This is either because data are no longer available or because data related to widely different stages of follow-up.

The lack of proven benefit of ICS may be due to the failure of clinical trials to provide the evidence for a benefit that does exist. The published trials of ICS have a number of flaws, which include small participant numbers, short treatment periods, inadequate drug dosages, and in one case the lack of a placebo group. The alternative view is that benefit has not been proven because there is no benefit. Delivering inhaled drugs in sufficient quantities to the airways which are blocked by viscous mucus may be a factor. Poor inhaler technique, especially in children, can also be a problem. More relevant may be the nature of the airway inflammation in CF. It is predominantly neutrophilic and in other airway conditions where neutrophils predominate, for example severe asthma and acute bronchiolitis, corticosteroids are also not particularly effective ([Green 2002](#); [Patel 2004](#)). Although there is proven benefit in certain aspects of COPD management ([NICE 2004](#)), a biopsy study showed that three months of fluticasone did not reduce the neutrophilic inflammation, despite improvement in symptoms and exacerbation rate ([Hattotuwa 2002](#)). Budesonide and fluticasone, and to a lesser extent beclomethasone, have been shown to prolong neutrophil survival by inhibiting apoptosis, so it might be that ICS are even promoting inflammation in CF airways ([Zhang 2001](#)).

Quality of the evidence

We were unable to combine data from the individual trials into a meta-analysis as the interventions were different between trials in terms of preparation, dosage and duration of treatment. This means that most of the evidence is reported narratively. Four of the included trials were reported only in abstract form with limited information available. We deemed the overall quality of the evidence to be either low or very low for a number of reasons. All outcomes were downgraded for risk of bias within the included studies as there were concerns around the clarity of the randomisation process and allocation concealment in some of the trials (although further information on this has been provided from some investigators) and issues with low participant numbers, selective reporting and publication bias.

Potential biases in the review process

In addition to carrying out a rigorous search of electronic databases, we scanned reference lists of included studies and contacted pharmaceutical companies for any unpublished trials in this area. We also searched trial registries for any additional ongoing studies. We feel it is unlikely that we have missed any trials. Two authors scanned titles and extracted data independently and assessed risk of bias to detect and minimise errors in data extraction or interpretation. The lead author for the review was also lead author on one of the included trials ([CF WISE 2006](#)), but data extraction and risk of bias assessment was carried out by a third author.

Agreements and disagreements with other studies or reviews

An important concern relates to the risk of acquisition of *P aeruginosa* infection in those treated with corticosteroids. Although one trial was halted prematurely out of this concern, the data available are not conclusive (Canadian Trial 1997). However, a retrospective study of 83 participants under 10 years of age, found no significant effect of the use of ICS on the risk of early *P aeruginosa* acquisition, including those on higher doses (Minicucci 2003).

Growth in childhood is always a concern with long-term corticosteroid use, and this includes inhaled corticosteroids. The Belgian trial has shown that one year of high-dose fluticasone adversely affected growth which did not catch up in the subsequent year (and in a subgroup followed for two years) (Belgian Trial 2007). However, the large difference in growth could have been due in part to the age difference between groups, 9.0 years for the placebo group and 8.2 years for the fluticasone group which might lead to a greater effect of pubertal growth over 24 months in the older (placebo) group. This was the first trial to look at growth over a reasonably long period and has provided important evidence that ICS can do harm in children with CF.

Finally, with regards to systemic adverse effects, there have been reports of children and adults with CF who developed adrenal insufficiency and sometimes Cushing's syndrome whilst taking ICS (400 to 1200 mcg/day) together with itraconazole for allergic bronchopulmonary aspergillosis, due to cytochrome P450 inhibition (Main 2002; Parmar 2002; Skov 2002).

AUTHORS' CONCLUSIONS

Implications for practice

Previous versions of this review have concluded that "evidence from these trials is insufficient to establish if inhaled corticosteroids have a beneficial or harmful effect in people with cystic fibrosis". The pendulum of risk/benefit has slowly swung towards risk with the publication of the Belgian Trial and away from benefit with the CF WISE 2006 (Belgian Trial 2007; CF WISE 2006). What is still not proven though is whether inhaled corticosteroids (ICS) can significantly reduce lung inflammation when given long term. This is important since if ICS slowed progression of cystic fibrosis (CF) lung disease, treatment should lead to improved morbidity and mortality. However, the downstream effects, i.e. lung function and symptoms, have not been shown to improve with ICS.

We conclude that the prescribing practice for an individual with CF should become more like that for an asthmatic and could be restricted to those with symptomatic recurrent wheezing that is not responsive to bronchodilators alone and in whom benefit has been proven. Justification is needed to start ICS, reassessment is necessary to see whether they are having an effect (particularly on any tight cough or wheeze), and consideration is always given to reducing the dose or stopping the drugs altogether. It is likely though that the majority of people with CF taking ICS no longer need to do so. This view has been reflected in the North American consensus document that states "...for patients with CF, 6 years and older, and without asthma or ABPA, the Cystic Fibrosis Foundation recommends against the routine use of inhaled corticosteroids to improve lung function and to reduce exacerbations" (Flume 2007). A similar view has been expressed in the consensus document from the European CF Society consensus meeting held in April 2008 (Heijerman 2009).

Implications for research

The principle unanswered question is whether long-term ICS can reduce the exuberant lung inflammation so common in people with CF, and whether they can slow the rate of decline in lung function and improve morbidity and mortality. Unfortunately it is unlikely that a randomised controlled trial with sufficient power and length of follow-up will be conducted, given the relatively small population of potential participants, difficulties with meaningful outcome measures (such as how to measure lung inflammation), financial limitations and research priorities in CF.

ACKNOWLEDGEMENTS

We are grateful to the Cochrane Cystic Fibrosis and Genetic Disorders Editorial Group for their support, to the investigators who provided additional unpublished information, to the referees of the review for useful comments and to Jeff Wagener for comments on an earlier version of this review.

We are also grateful to Carol Dezateux for her input as an author on previous versions of this review, and to Sarah Walters who had the original idea for the review, drafted the protocol, extracted data and co-authored earlier versions of the review.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Austrian Trial 1995 {published data only}

Eichler I, Wojnarowski C, Frischer T, Renner S, Koller DY, Gotz M. Inhaled corticosteroids suppress increased eosinophil cationic protein concentration in patients with cystic fibrosis. *Pediatric Pulmonology* 1995;**Suppl 12**:326. [CFGD REGISTER: IB14a]

* Wojnarowski C, Götz M, Eichler HG, Frischer T, Renner S, Koller DY, et al. Inhaled corticosteroids suppress inflammation in patients with cystic fibrosis. In: Proceedings of the 20th European Cystic Fibrosis Conference; 1995 June 18-21; Brussels, Belgium. 1995:Poster P98. [CENTRAL: 291657] [CFGD REGISTER: IB14b]

Wojnarowski C, Gotz M, Eichler HG, Frischer T, Koller DY, Eichler I. Topical steroid act anti-inflammatorily by patients with cystic fibrosis. *Monatsschrift Fur Kinderheilkunde* 1995;**143**:218. [CFGD REGISTER: IB14c]

Belgian Trial 2007 {published data only}

De Boeck K, De Baets F, Malfroot A, Desager K, Mouchet F, Proesmans M. Do inhaled corticosteroids impair long-term growth in prepubertal cystic fibrosis patients? *European Journal of Pediatrics* 2007;**166**(1):23-8. [CFGD REGISTER: IB49]

Canadian Trial 1997 {published data only}

Schmidt J, Davidson AGF, Seear M, Wong LTK, Peacock D, Gravelle A et al. Is the acquisition of pseudomonads in cystic fibrosis patients increased by use of inhaled corticosteroids? Unexpected results from a double blind placebo controlled study. *Pediatric Pulmonology* 1997;**Suppl 14**:293. [CFGD REGISTER: IB18]

CF WISE 2006 {published data only}

Balfour-Lynn IM, Lees B, Hall P, Phillips G, Khan M, Flather M, et al. CF WISE - Multicentre randomised controlled trial of withdrawal of inhaled corticosteroids. *Pediatric Pulmonology* 2005;**40**(Suppl 28):123-4. [CFGD REGISTER: IB48a]

* Balfour-Lynn IM, Lees B, Hall P, Phillips G, Khan M, Flather M, et al. Multicenter randomized controlled trial of withdrawal of inhaled corticosteroids in cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2006;**173**(12):1356-62. [CFGD REGISTER: IB48b]

Danish Trial 1983 {published data only}

Schiotz P, Jorgensen M, Winge Flensburg E, Fero O, Husby S, Hoiby N et al. A longitudinal study of immune complex activity and inflammatory response in sputum sol-phase of CF patients: influence of local steroid treatment. In: Proceedings of the 11th European Cystic Fibrosis Conference; 1982; Brussels. 1982:51. [CFGD REGISTER: IB1b]

* Schiotz PO, Jorgensen M, Flensburg EW, Faero O, Husby S, Hoiby N, et al. Chronic *Pseudomonas aeruginosa* lung infection in cystic fibrosis. A longitudinal study of immune complex activity and inflammatory response in sputum sol-phase of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infections: influence of local steroid treatment. *Acta*

Paediatrica Scandinavica 1983;**72**(2):283-7. [CENTRAL: 30682] [CFGD REGISTER: IB1a] [PMID: 6340415]

Danish Trial 1997 {published data only}

Bisgaard H, Nielson K H, Sov M, Mosfeldt E, Bjerre B, Pedersen S et al. Inhaled steroid treatment of CF patients with chronic pseudomonas aeruginosa (P.a.) lung infection. *Pediatric Pulmonology* 1994;**18**(Suppl 10):395. [CFGD REGISTER: IB12a]

* Bisgaard H, Pedersen SS, Nielsen KG, Skov M, Laursen EM, Kronborg G et al. Controlled trial of inhaled budesonide in patients with cystic fibrosis and chronic bronchopulmonary pseudomonas aeruginosa infection. *American Journal of Respiratory and Critical Care Medicine* 1997;**156**(4 Pt 1):1190-6. [CFGD REGISTER: IB12c]

Bisgaard H, Petersen SS, Nielsen KG. Topical steroid treatment ameliorate lung pathophysiology of patients with cystic fibrosis and chronic pseudomonas AER. *European Respiratory Journal* 1996;**9**(Suppl):174S. [CFGD REGISTER: IB12b]

Dutch Trial 1995 {published data only}

van Haren EH, Lammers JW, Festen J, Heijerman HG, Groot CA, van Herwaarden CL. The effects of the inhaled corticosteroid budesonide on lung function and bronchial hyperresponsiveness in adult patients with cystic fibrosis. *Respiratory Medicine* 1995;**89**(3):209-14. [CFGD REGISTER: IB9]

German Trial 1999 {published data only}

Dauletbaev N, Viel K, Behr J, Loitsch S, Buhl R, Wagner TOF, Bargon J. Effects of short-term inhaled fluticasone on oxidative burst of sputum cells in cystic fibrosis patients. *European Respiratory Journal* 1999;**14**(5):1150-5. [CFGD REGISTER: IB26]

Irish Trial 1995 {published data only}

* Hayes J, Cosgrave C, O'Connor C, FitzGerald M. The effect of high dose inhaled corticosteroids on levels of sputum of plasma elastase and IL8 in patients with mild cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* 1995;**151**(4 Suppl):A248. [CFGD REGISTER: IB8a]

Hayes J, Cosgrave C, O'Connor C, FitzGerald MX. The effect of high dose inhaled corticosteroids on levels of sputum or plasma elastase IL-8 in patients with mild cystic fibrosis. *Irish Journal of Medical Science* 1995;**164**(2):165. [CFGD REGISTER: IB8b]

Swiss Trial 1996 {published data only}

Nikolaizik WH, Schoni MH. Effect of inhaled corticosteroids on lung function of cystic fibrosis patients - a prospective study. *European Respiratory Journal* 1994;**7**:430S. [CFGD REGISTER: IB15b]

* Nikolaizik WH, Schoni MH. Pilot study to assess the effect of inhaled corticosteroids on lung function in patients with cystic fibrosis. *Journal of Pediatrics* 1996;**128**(2):271-4. [CFGD REGISTER: IB15c]

Schöni MH, Nikolaizik. Parallel group study to assess the effect of inhaled corticosteroids on lung function in patients with cystic fibrosis. *Israel Journal of Medical Sciences*

1996;**32**(Suppl):S190. [CENTRAL: 291577] [CFGD REGISTER: IB15a]

Turkish Trial 2017 {published data only}

Uyan ZS, Unluguzel G, Haklar G, Cakir E, Oktem S, Ersu R, et al. The effect of inhaled steroids on bronchial hyperreactivity, oxidative status, clinical and inflammatory parameters in patients with cystic fibrosis. In: Proceedings of European Respiratory Society Annual Congress; 2007 Sep 15-19; Stockholm, Sweden. 2007:646s. [CFGD REGISTER: IB50b]

Uyan ZS, Unluguzel G, Haklar G, Cakir E, Oktem S, Ersu R, et al. The effect of inhaled steroids on bronchial hyperreactivity, oxidative status, clinical and inflammatory parameters in patients with cystic fibrosis. *Journal Cystic Fibrosis* 2008;**7**(Suppl 2):S68. [CFGD REGISTER: IB50a]

* Uyan ZS, Unluguzel Ustun G, Haklar G, Cakir E, Oktem S, Ersu R, et al. Effect of inhaled steroids on clinical and inflammatory parameters in children with cystic fibrosis. *Turkish Journal of Medical Sciences* 2017;**47**(5):1432-40. [CFGD REGISTER: IB50c]

UK Trial 1996 {published data only}

Nieman R, Williams S, Maden C, Knight R, Hodson M. A double-blind placebo-controlled study comparing the effects of the inhaled corticosteroid fluticasone propionate 500 mcg BID with placebo in adults with cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* 1996;**153**:A72. [CFGD REGISTER: IB16]

UK Trial 1997 {published data only}

Balfour-Lynn I, Klein N J, Dinwiddie R. Sputum Interleukin-10 in cystic fibrosis. *Pediatric Pulmonology* 1996;**22**(Suppl 13):324. [CFGD REGISTER: IB17b]

* Balfour-Lynn I, Klein N J, Dinwiddie R. Randomised controlled trial of inhaled corticosteroids (fluticasone propionate) in cystic fibrosis. *Archives of Disease in Childhood* 1997;**77**(2):124-30. [CFGD REGISTER: IB17d]

Balfour-Lynn IM, Klein NJ, Dinwiddie R. Trial of inhaled corticosteroids (Fluticasone Propionate) in children with cystic fibrosis(CF). *Israel Journal of Medical Sciences* 1996;**32**(Suppl):S190. [CENTRAL: 291194] [CFGD REGISTER: IB17a]

Balfour-Lynn IM, Klein NJ, Laverty A, Dinwiddie R. Effect of inhaled corticosteroids on airway nitric oxide levels in children with CF. *Pediatric Pulmonology* 1996;**Suppl 13**:324. [CFGD REGISTER: IB17c]

References to studies excluded from this review

Australia Trial 2000 {published data only}

McElrea MS, O'Donnell SR, Francis PW. The effects of high-dose inhaled beclomethasone dipropionate (BDP) on lung function and sputum albumin in children with cystic fibrosis (CF). *Pediatric Pulmonology* 2000;**30**(Suppl 20):301. [CFGD REGISTER: IB31]

Bessaci 2008 {published data only}

Bessaci K, Milliot M, Zahm J, Vilprey M, Coraux C, Mauran P, et al. Effects of inhaled association of salmeterol-fluticasone propionate on lung and epithelial cell functions in cystic fibrosis children. *Pediatric Pulmonology* 2008;**43**(Suppl 31):384. [CFGD REGISTER: IB51b]

Bessaci K, Milliot M, Zahm JM, Coraux C, Mauran P, Vitry F, et al. Effects of inhaled salmeterol-fluticasone propionate on lung and epithelial cell functions in cystic fibrosis children: a double blind crossover study. *Journal of Cystic Fibrosis* 2008;**7**(Suppl 2):S66. [CFGD REGISTER: IB51a]

USA Trial 1996 {published data only}

* Wojtczak HA, Kerby GS, Wagener JS, Copenhaver SC, Gotlin RW, Riches DW et al. Beclomethasone dipropionate reduced airway inflammation without adrenal suppression in young children with cystic fibrosis: a pilot study. *Pediatric Pulmonology* 2001;**32**(4):293-302.

Wojtczak HA, Wagener JS, Kerby G, Gotlin R, Accurso F. Effect of inhaled beclomethasone dipropionate on airway inflammation in children with cystic fibrosis. *Pediatric Pulmonology* 1996;**22**(Suppl 13):323-4.

USA Trial 1998 {published data only}

* Wojtczak HA, Sontag MK, Wagener JS, Accurso FJ. Inhaled corticosteroid treatment in infants and young children with cystic fibrosis. *Pediatric Pulmonology* 1999;**28**(Suppl 19):105-6. [CFGD REGISTER: IB22b]

Wojtczak HA, Wagener JS, Sontag MK, Accurso FJ. Bronchoalveolar lavage assessment of airway delivery of fluticasone propionate via pressurised metered dose inhaler in infants and young children with cystic fibrosis. *Pediatric Pulmonology* 1998;**19**:341. [CFGD REGISTER: IB22a]

References to studies awaiting assessment

Kapustina 2008 {published data only}

Kapustina T, Fedorova V, Voronkova A, Kapranov N. Long-term treatment with corticosteroids and bone mineral density in patients with cystic fibrosis. In: Proceedings of the European Respiratory Society Annual Congress; 2008 Oct 4-8; Berlin, Germany. 2008:214s. [CFGD REGISTER: IB94]

Additional references

ABPI 1999

Association of the British Pharmaceutical Industry. Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000. London: Datapharm Publications Ltd, 1999.

Armstrong 1995

Armstrong DS, Greenwood K, Carzino JB, Olinsky A, Phelan PD. Lower respiratory infection and inflammation in infants with newly-diagnosed cystic fibrosis. *BMJ* 1995;**310**(6994):1570-72.

Balfour-Lynn 1999

Balfour-Lynn IM, Dezateux C. Corticosteroids and ibuprofen in cystic fibrosis (letter). *Thorax* 1999;**54**(7):657.

Balfour-Lynn 2002

Balfour-Lynn IM, Elborn JS. "CF asthma": what is it and what do we do about it? *Thorax* 2002;**57**:742-8.

Balfour-Lynn 2007

Balfour-Lynn IM. Anti-inflammatory approaches to cystic fibrosis airways disease. *Current Opinion in Pulmonary Medicine* 2007;**13**:522-8.

Balfour-Lynn 2008

Balfour-Lynn IM. Personal communication with UK CF Trust and CFF October 2008.

Balough 1995

Balough K, McCubbin M, Weinberger M, Smits W, Ahrens R, Fick R. The relationship between infection and inflammation in the early stages of lung disease from cystic fibrosis. *Pediatric Pulmonology* 1995;**20**(2):63-70.

Barnes 1992

Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. Report of a workshop held in Eze, France, October 1992. *American Review of Respiratory Disease* 1993;**148**(4 Pt 2):S1-26.

Booth 1995

Booth H, Richmond I, Ward C, Gardiner PV, Harkawat R, Walters EH. Effect of high dose inhaled fluticasone propionate on airway inflammation in asthma. *American Journal of Respiratory and Critical Care Medicine* 1995;**152**(1):45-52.

Burdon 1980

Burdon JG, Cade JF, Sutherland PW, Pain MC. Cystic fibrosis and bronchial hyperreactivity: concomitant defects or cause and effect? *Medical Journal of Australia* 1980;**2**(2):77-8.

Calpin 1997

Calpin C, Macarthur C, Stephens D, Feldman W, Parkin PC. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systemic review of the literature. *Journal of Allergy and Clinical Immunology* 1997;**100**(4):452-7.

Cheng 1999

Cheng K, Ashby, Smyth R. Oral steroids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 1999, Issue 4. Art. No: CD000407. [DOI: [10.1002/14651858.CD000407.pub2](https://doi.org/10.1002/14651858.CD000407.pub2)]

Djukanovic 1992

Djukanovic R, Wilson JW, Britten KM, Wilson SI, Walls AF, Roche WR et al. Effect of an inhaled corticosteroid on airway inflammation and symptoms in asthma. *American Review of Respiratory Disease* 1992;**145**(3):669-74.

Drake 2002

Drake AJ, Howells RJ, Shield JPH, Prendiville A, Ward PS, Crowne PC. Symptomatic adrenal insufficiency presenting with

hypoglycaemia in children with asthma receiving high dose inhaled fluticasone propionate. *BMJ* 2002;**324**(7345):1081-2.

Elbourne 2002

Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analysis involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**:140-9.

Flume 2007

Flume PA, O'Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ Jr, Willey-Courand DB, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *American Journal of Respiratory and Critical Care Medicine* 2007;**176**(10):957-69.

Green 2002

Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax* 2002;**57**(10):875-79.

Hattotuwa 2002

Hattotuwa KL, Gizycki MJ, Ansari TW, Jeffery PK, Barnes NC. The effects of inhaled fluticasone on airway inflammation in chronic obstructive pulmonary disease: a double-blind, placebo-controlled biopsy study. *American Journal of Respiratory and Critical Care Medicine* 2002;**165**(12):1592-6.

Heijerman 2009

Heijerman H, Westerman E, Conway S, Touw D, Döring G, consensus working group. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: A European consensus. *Journal of Cystic Fibrosis* 2009;**8**(5):295-315. [DOI: [10.1016/j.jcf.2009.04.005](https://doi.org/10.1016/j.jcf.2009.04.005)]

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, editors(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.

Hilliard 2005

Hilliard TN, Balfour-Lynn IM. Anti-inflammatory agents a clinical perspective. In: Bush A, editors(s). *Progress in Respiratory Research Cystic Fibrosis*. Basel: S Karger AG, 2005:187-94.

Khan 1995

Khan TZ, Wagner JS, Bost T, Martinez J, Accurso FJ, Riches DW. Early pulmonary inflammation in infants with cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* 1995;**151**(4):1975-82.

Koch 1997

Koch C, McKenzie SG, Kaplowitz H, Hodson ME, Harms HK, Navarro J et al. International practice patterns by age and

severity of lung disease in cystic fibrosis: data from the Epidemiologic Registry of Cystic Fibrosis (ERCF). *Pediatric Pulmonology* 1997;**24**(2):147-154.

Koehler 2004

Koehler DR, Downey GP, Sweezey NB, Tanswell AK, Hu J. Lung inflammation as a therapeutic target in cystic fibrosis. *American Journal of Respiratory Cell and Molecular Biology* 2004;**31**(4):377-81.

Konstan 1994

Konstan MW, Hilliard KA, Norvell EM, Berger M. Bronchoalveolar lavage findings in cystic fibrosis patients with stable, clinically mild lung disease suggest ongoing infection and inflammation. *American Journal of Respiratory and Critical Care Medicine* 1994;**150**(2):448-54.

Konstan 1999

Konstan MW, Butler SM, Schidlow DV, Morgan WJ, Julius JR, Johnson CA, for the Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Patterns of medical practice in cystic fibrosis: Part II. Use of therapies. *Pediatric Pulmonology* 1999;**28**(4):248-54.

Lipworth 1999

Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Archives of Internal Medicine* 1999;**159**(9):941-55.

Macedessi 2003

Macedessi JS, Randell TL, Donaghue KC, Ambler GR, Van Asperen PP, Mellis CM. Adrenal crises in children treated with high-dose inhaled corticosteroids for asthma. *Medical Journal of Australia* 2003;**178**(5):214-6.

Main 2002

Main KM, Skov M, Sillesen IB, Dige-Petersen H, Muller J, Koch C, et al. Cushing's syndrome due to pharmacological interaction in a cystic fibrosis patient. *Acta Paediatrica* 2002;**91**(9):1008-11.

Minicucci 2003

Minicucci L, Severi G, Cresta L, Giannattasio A, Lorini R, Haupt R. Impact of inhaled corticosteroids on the risk of early *Pseudomonas aeruginosa* acquisition in cystic fibrosis. *Acta Paediatrica* 2003;**92**(6):684-7.

Mitchell 1978

Mitchell I, Corey M, Woenne R, Krastins IR, Levison H. Bronchial hyperreactivity in cystic fibrosis and asthma. *Journal of Pediatrics* 1978;**93**(5):744-8.

NICE 2004

National Institute for Clinical Excellence (NICE). Chronic obstructive pulmonary disease: national clinical guideline for management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004;**59**(Suppl 1).

Parmar 2002

Parmar JS, Howell T, Kelly J, Bilton D. Profound adrenal suppression secondary to treatment with low dose inhaled

steroids and itraconazole in allergic bronchopulmonary aspergillosis in cystic fibrosis. *Thorax* 2002;**57**(8):749-50.

Patel 2001

Patel L, Wales JK, Kibirige MS, Massarano AA, Couriel JM, Clayton PE. Symptomatic adrenal insufficiency during inhaled corticosteroid treatment. *Archives of Disease in Childhood* 2001;**85**(4):330-4.

Patel 2004

Patel H, Platt R, Lozano JM, Wang EEL. Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No: CD004878. [DOI: [10.1002/14651858.CD004878.pub2](https://doi.org/10.1002/14651858.CD004878.pub2)]

Renkema 1996

Renkema TE, Schouten UP, Koeter GH Postma DS. Effects of long-term treatment with corticosteroids in COPD. *Chest* 1996;**109**(5):1156-62.

Russell 2004

Russell G. The use of inhaled corticosteroids during childhood: plus ca change. *Archives of Disease in Childhood* 2004;**89**(10):893-5.

Schünemann 2006

Schünemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 9. Grading evidence and recommendations. *Health Research Policy Systems* 2006;**4**:21.

Schünemann 2011

Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration. Available from www.cochrane-handbook.org 2011.

Skov 2002

Skov M, Main KM, Sillesen IB, Muller J, Koch C, Lanng S. Iatrogenic adrenal insufficiency as a side-effect of combined treatment of itraconazole and budesonide. *European Respiratory Journal* 2002;**20**(1):127-33.

Smeeth 2003

Smeeth L, Boulis M, Hubbard R, Fletcher AE. A population based case-control study of cataract and inhaled corticosteroids. *British Journal of Ophthalmology* 2003;**87**(10):1247-51.

Taylor 1999

Taylor AV, Laoprasert N, Zimmerman D, Sachs MI. Adrenal suppression secondary to inhaled fluticasone propionate. *Annals of Allergy, Asthma & Immunology* 1999;**83**(1):68-70.

Tobin 1980

Tobin MJ, Maguire D, Keen D, Tempany E, Fitzgerald MX. Atopy and bronchial reactivity in older patients with cystic fibrosis. *Thorax* 1980;**35**(11):807-13.

Todd 1996

Todd G, Dunlop K, McNaboe J, Ryan MF, Carson D, Shields MD. Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate. *Lancet* 1996;**348**(9019):27-9.

Todd 2002

Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Archives of Disease in Childhood* 2002;**87**(6):457-61.

van Grunsven 1999

van Grunsven PM, van Schayck CP, Molema J, Akkermans RP, van Weel C. Effect of inhaled corticosteroids on bronchial responsiveness in patients with "corticosteroid naive" mild asthma: a meta-analysis. *Thorax* 1999;**54**(4):316-22.

Walters 1995

Walters S. Association of cystic fibrosis adults (UK) Survey 1994 - Analysis and Report. Cystic Fibrosis Trust 1995.

Walters 2001

Walters S. Personal communication June 14 2001.

Weir 1993

Weir DC, Burge PS. Effects of high dose inhaled beclomethasone dipropionate 750 micrograms and 1500 micrograms twice daily and 40 mg per day oral prednisolone on lung function, symptoms and bronchial hyperresponsiveness in patients with non-asthmatic chronic airflow obstruction. *Thorax* 1993;**48**(4):309-16.

Zhang 2001

Zhang X, Moilanen E, Kankaanranta H. Beclomethasone, budesonide and fluticasone propionate inhibit human neutrophil apoptosis. *European Journal of Pharmacology* 2001;**431**(3):365-71.

References to other published versions of this review

Balfour-Lynn 2000

Balfour-Lynn I, Walters S, Dezateux C. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2000, Issue 1. Art. No: CD001915. [DOI: [10.1002/14651858.CD001915](https://doi.org/10.1002/14651858.CD001915)]

Balfour-Lynn 2009

Balfour-Lynn IM, Welch K. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No: CD001915. [DOI: [10.1002/14651858.CD001915.pub2](https://doi.org/10.1002/14651858.CD001915.pub2)]

Balfour-Lynn 2012

Balfour-Lynn IM, Welch K. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No: CD001915. [DOI: [10.1002/14651858.CD001915.pub3](https://doi.org/10.1002/14651858.CD001915.pub3)]

Balfour-Lynn 2014

Balfour-Lynn IM, Welch K. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2014, Issue 10. Art. No: CD001915. [DOI: [10.1002/14651858.CD001915.pub4](https://doi.org/10.1002/14651858.CD001915.pub4)]

Balfour-Lynn 2016

Balfour-Lynn IM, Welch K. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2016, Issue 8. Art. No: CD001915. [DOI: [10.1002/14651858.CD001915.pub5](https://doi.org/10.1002/14651858.CD001915.pub5)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Austrian Trial 1995

Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial. Design: parallel. Duration: 22 weeks (preceded with 2-week run in). Location: single centre in Austria.
Participants	15 CF participants with acute pulmonary exacerbation. Age not given (but was in a paediatric department).
Interventions	All participants given a 2-week course of intravenous antibiotics. Intervention group: beclomethasone 500 mcg 3x daily administered by large volume spacer. Control group: placebo.

Inhaled corticosteroids for cystic fibrosis (Review)

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Austrian Trial 1995 (Continued)

Outcomes	Serum eosinophil cationic protein. Myeloperoxidase.
Notes	Authors contacted: no reply. Trial not published in full (3 abstracts) - all available information on methodological quality, as presented in primary paper, is reported here.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No figures.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported.
Other bias	Unclear risk	Trial had never been published in a peer-reviewed journal.

Belgian Trial 2007

Study characteristics

Methods	Randomised, double-blind, controlled trial. Design: parallel. Duration: 12 months. Location: multicentre in Belgium.
Participants	29 pre-pubertal children (20 from 1 centre and 9 from another centre) who were clinically stable (defined as at least 2 months after any hospital admission and 2 weeks after a respiratory exacerbation) with FEV ₁ at least 60% predicted. Excluded if had intake of oral or inhaled steroids for more than 2 weeks within past 6 months or any intake of these drugs including intranasal steroids within last 4 weeks or a clinical diagnosis of aspergillosis or participating in another clinical trial.
Interventions	Intervention group: fluticasone 500 mcg dry powder inhaler twice daily. Control group: lactose placebo twice daily (dispensed in identical canister).
Outcomes	Change in % predicted FEV ₁ and change in FEV ₁ L 20 minutes after inhalation of 400 mcg salbutamol by large plastic spacer device.

Belgian Trial 2007 (Continued)

Serum IgG levels.

Brasfield chest X-ray scores.

Number of respiratory exacerbations.

Positive *P aeruginosa* culture.

Height.

Notes Of the 20 initially included participants 2 were excluded. 1 participant discontinued treatment after 3 months and 1 did not keep follow-up appointments.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated that used random number sequence.
Allocation concealment (selection bias)	Unclear risk	Not mentioned in text.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded. Placebo dispensed in identical canister, so probably participant and clinician blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 15% of participants were excluded. Of the 20 initially included participants, 2 were excluded (1 discontinued treatment after 3 months and 1 did not keep follow-up appointments).
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	No other potential source of bias identified.

Canadian Trial 1997

Study characteristics

Methods	<p>Randomised, double-blind, placebo-controlled trial.</p> <p>Design: parallel.</p> <p>Duration: proposed 1 year; all variables measured at baseline and at 3-monthly intervals throughout the trial, duration of follow up was 9 months.</p> <p>Location: single centre in Vancouver, Canada.</p>
Participants	<p>17 (9 male) participants, clinically diagnosed people with CF, aged 6 - 17 years attending the CF clinic at British Columbia Children's Hospital, Vancouver.</p> <p>Mean age 7.5 years in fluticasone group and 9.2 years in placebo group.</p>
Interventions	<p>Intervention group: fluticasone 500 mcg twice daily via a metered dose inhaler and aerosol spacer.</p> <p>Control group: matched placebo twice daily via a metered dose inhaler and aerosol spacer.</p>

Canadian Trial 1997 (Continued)

Outcomes	Lung function (FEV ₁ , FVC, FEF ₂₅₋₇₅). Oxygen saturation. Sputum or throat bacteriology. Weight. Height. Clinical status.
Notes	Trial was halted prematurely because of concerns about possible increased frequency of pulmonary colonisation with <i>P aeruginosa</i> among participants. Authors contacted: confirmed that written informed consent was obtained; provided age and sex distribution and lung function data by group. Trial not published in full (1 abstract).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised in blocks of 4, but method of randomisation not stated.
Allocation concealment (selection bias)	Low risk	Sealed envelopes used.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded. Fluticasone or matched placebo delivered in same way.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Trialists provided data to authors as requested.
Selective reporting (reporting bias)	High risk	Clinical status and nutritional indices were specified as outcomes in the Canadian trial but have not been reported to date.
Other bias	Unclear risk	Trial was halted prematurely and trial results have never been published in a peer-reviewed journal.

CF WISE 2006

Study characteristics

Methods	Randomised, double-blind, placebo-controlled withdrawal trial. Design: parallel. Duration: 8 months (including a 2 month run-in period). Location: multicentre (18 paediatric and adult centres) in UK.
Participants	Eligibility - age over 6 years, FEV ₁ ≥ 40% predicted.

CF WISE 2006 (Continued)

	<p>Participants excluded if had used oral corticosteroids within the previous 3 months or very high dose of ICS.</p> <p>171 (86 male) participants randomised.</p> <p>Diagnosed with CF.</p> <p>Age range 6 - 53 years; mean age 14 years in fluticasone group and 15.8 years in placebo group.</p>
Interventions	<p>Intervention group: fluticasone propionate given via a volumatic spacer at equivalent dose to ICS participant taking before trial entry.</p> <p>Control group: placebo given via a volumatic spacer.</p>
Outcomes	<p>Primary outcome</p> <p>Time to first respiratory exacerbation.</p> <p>Secondary outcomes</p> <p>Lung function (FEV₁, FVC)</p> <p>Unplanned courses of intravenous or oral antibiotics.</p> <p>Rescue bronchodilator usage.</p> <p>Subgroup analysis - age, atopy, steroid dose, baseline FEV₁, Pseudomonas status.</p>
Notes	<p>2 month run-in period during which all participants received fluticasone propionate. Dose unchanged if previously receiving fluticasone, but if previously on budesonide or beclomethasone, this was changed to fluticasone at a 2:1 ratio.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Local investigators recruited participants in each centre and then telephoned a dedicated randomisation service at the Royal Brompton Hospital Clinical Trials and Evaluation Unit to give participant details. Randomisation was performed in permuted blocks of 4 to balance the stratifying variables and centres. Participants were stratified for age (< 17 or ≥ 17 years), FEV ₁ (40% - 60%, 61 - 80% and > 80% predicted), and atopic status (yes/no). Participants were randomised in equal proportions to withdrawal of fluticasone and non-withdrawal of fluticasone.
Allocation concealment (selection bias)	Low risk	Randomisation was carried out independently at the Clinical Trials & Evaluation Unit of Royal Brompton Hospital and allocation of individuals was carried out over the telephone to the trial centres. The trial drug randomisation number was given to the investigator and faxed to the Pharmacy department at the Royal Brompton Hospital who then sent out the corresponding drug pack to the pharmacy at the local hospital, which provided it to the participant.
Blinding (performance bias and detection bias) All outcomes	Low risk	All trial personnel and participants were blinded to treatment (placebo).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was based on all participants.

CF WISE 2006 (Continued)

Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other potential source of bias identified.

Danish Trial 1983
Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial. Design: parallel. Duration: 16 weeks. Location: Denmark.
Participants	48 CF participants (29 male) including children and adults age 4 - 29 years with a 'typical history of CF and markedly elevated sweat electrolytes in repeated tests'. Matched in pairs according to clinical score and, if possible, age and sex. Chronic <i>P aeruginosa</i> lung infections for more than 6 months with 2 or more serum pseudomonal precipitins.
Interventions	Intervention group: beclomethasone 400 mcg 4x daily via metered dose inhaler. Control group: placebo 4x daily via metered dose inhaler. Treatment started on last day of 2-week course of intravenous carbenicillin and tobramycin given as hospital inpatient.
Outcomes	Lung function (PEFR, FVC). Chest X-ray score. Blood tests (erythrocyte sedimentation rate, white blood count, serum immunoglobulins, serum albumin, serum haptoglobin, serum pseudomonal precipitins before and after treatment in both groups).
Notes	Authors contacted: participants matched in pairs by clinical score and randomised within pairs, but allocation concealment remains unclear; informed verbal consent given; data provided on age and sex distribution but not lung function. Original data no longer available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants matched in pairs by clinical score and randomised within pairs. Method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	No details available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded.

Danish Trial 1983 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	More than 15% of participants were excluded, but reasons given and numbers equal across groups. 5 participants (3 in the beclomethasone group) withdrawn because of clinical deterioration and started on beclomethasone. A further 6 either did not attend the control examination at clinic or discontinued inhalation therapy. As none from same matched pair data analysis carried out on 13 pairs (26 participants) only.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other potential source of bias identified.

Danish Trial 1997

Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial. Design: parallel. Duration: 6 months (with 2-week elective course of intravenous antibiotics given at start and between both 3-month treatment periods). Location: Denmark.
Participants	Eligibility criteria: age 8 years and over; continuous isolation of <i>P aeruginosa</i> for at least 6 months or significant increase (not defined) in serum anti-pseudomonas antibodies. Excluded if asthma, allergic bronchopulmonary aspergillosis; colonisation with <i>Burkholderia cepacia</i> , pregnant, severely impaired cardiac, hepatic or renal function (not defined); treated with inhaled or oral steroids in previous 2 months. 55 participants, clinically diagnosed with CF randomised. Mean age 29 years.
Interventions	Intervention group: budesonide 800 mcg twice daily as a dry powder inhaled through a spacer device. Control group: lactose powder inhaled through a spacer device. Given as 2 consecutive treatment periods each of 3 months duration with 2-week elective course of intravenous antibiotics given at start and between 2 treatment periods.
Outcomes	Lung function (FEV ₁ , FVC). Bronchial reactivity assessed by histamine PC ₂₀ and exercise test. Sputum inflammatory markers (tumour necrosis factor, interleukin-1 receptor antagonist, polymorphonuclear granulocyte elastase, free elastolytic activity; plasma inflammatory markers: polymorphonuclear granulocyte elastase, precipitating antibodies against <i>P aeruginosa</i>); adrenal function (ACTH stimulation test) in those under 18 years; compliance (assessed by counting number of doses left in Turbuhalers at each clinic visit); adverse effects (hoarse voice, oral thrush, haemoptysis, cough, pneumothorax, chest pain, abscess, pharyngitis, pneumonia, infection or fever).

Danish Trial 1997 (Continued)

Notes	Randomised in balanced blocks of 4 participants.
	Treatment codes were not broken before clean file was declared by the data manager according to GCP recommendations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised in balanced blocks of 4 participants. Method of randomisation not stated.
Allocation concealment (selection bias)	Low risk	Stated that treatment codes were not broken before clean file was declared by the data manager according to GCP recommendations.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysed on both an 'intention-to-treat' and 'completed treatment' basis. Participants considered not to have completed treatment if period between intravenous courses was < 8 weeks or > 20 weeks or if sum of 2 treatment periods < 18 weeks or > 40 weeks.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	No other potential source of bias identified.

Dutch Trial 1995

Study characteristics

Methods	Double-blind, placebo-controlled trial. Design: cross-over. Duration: 6 weeks (run in period of 2 weeks, but no washout period). Location: the Netherlands.
Participants	Exclusion criteria: pregnant, currently taking oral steroids, severe concomitant disease. 16 participants with CF randomised, diagnosed by sweat test. Age: mean age 27 years; range 16 - 45 years). Baseline FEV ₁ > 25% predicted, no acute pulmonary exacerbation in previous 6 weeks. PC20 FEV ₁ histamine < 16 mg/mL.
Interventions	Participants stopped sodium cromoglycate, antihistamines and theophylline preparations before trial. Intervention group: budesonide 200 mcg per puff, given as 4 puffs (800 mcg) twice daily via blinded metered-dose inhalers supplied by pharmaceutical company.

Dutch Trial 1995 (Continued)

Control group: placebo given as 4 puffs twice daily given by blinded metered-dose inhalers supplied by pharmaceutical company.

Outcomes	<p>Lung function tests (FEV₁, FVC, twice-daily peak expiratory flow rates).</p> <p>Bronchial reactivity (histamine provocation).</p> <p>Hospital admissions for respiratory exacerbations.</p> <p>Antibiotic use.</p> <p>Symptom diary.</p>
Notes	<p>Written to first author but left department with no forwarding details.</p> <p>All available information on methodological quality, as presented in primary paper, is reported here.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed.
Allocation concealment (selection bias)	Low risk	Budesonide or placebo given by blinded metered-dose inhalers supplied by pharmaceutical company.
Blinding (performance bias and detection bias) All outcomes	Low risk	<p>Described as double-blind, but no details of who exactly was blinded.</p> <p>Budesonide or placebo given for 6 weeks by blinded metered-dose inhalers.</p>
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear.
Selective reporting (reporting bias)	High risk	Hospital admissions and antibiotic usage were specified as outcomes, but no data were reported.
Other bias	Unclear risk	No washout period described.

German Trial 1999

Study characteristics

Methods	<p>Randomised, open-labelled trial.</p> <p>Design: parallel.</p> <p>Duration: 6 weeks.</p> <p>Location: Germany.</p>
Participants	<p>26 adults (13 males) with 'stable' CF.</p> <p>Age; median age 26 years; range 16 years to 38 years.</p> <p>None on oral steroids and no ICS within 6 weeks.</p>

German Trial 1999 (Continued)

Interventions	Intervention group: fluticasone propionate 500 mg twice daily as dry powder inhaler. Control group: non-steroid medication.
Outcomes	Lung function tests (FEV ₁ , FVC, MEF ₂₅₋₇₅). Sputum (leukocyte count, myeloperoxidase activity, baseline and stimulated superoxide anion release). Self-reported symptoms elicited by questionnaire.
Notes	Author contacted with request for information regarding allocation concealment and numbers of participants included in analysis of FEV ₁ outcome.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Prior to the trial, a random number row was generated, and participants with even and odd numbers were consecutively divided into the treatment and control groups. Low risk of bias because first participant allocated from random number row.
Allocation concealment (selection bias)	High risk	Alternation used - risk of bias as investigators could foresee which group next participant would be allocated to.
Blinding (performance bias and detection bias) All outcomes	High risk	Open label.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	No other potential source of bias identified.

Irish Trial 1995

Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial. Design: cross-over. Duration: 4 weeks with 4-week washout period. Location: Ireland.
Participants	7 adults (4 male) with mild CF. % predicted FEV ₁ , mean (SE): 85.4% (6.4). % predicted FVC, mean (SE): 95.7% (6.4).

Irish Trial 1995 (Continued)

All grew *P aeruginosa* in sputum; 2 participants atopic (not defined).

Interventions	Intervention group: beclomethasone 1500 mcg daily. Control group: matched placebo.
Outcomes	Spirometry and bronchial reactivity measured by methacholine challenge. Markers of inflammation in blood and sputum (alpha one protease inhibitor, neutrophil elastase and interleukin 8).
Notes	Authors contacted: randomisation by 'envelope'; no full publication; no additional data provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation by 'envelope'.
Allocation concealment (selection bias)	Low risk	Sealed envelopes used.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was based on all participants.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the abstract.
Other bias	Unclear risk	Trial has never been published in a peer-reviewed journal.

Swiss Trial 1996

Study characteristics

Methods	Randomised controlled trial. Design: parallel. Duration: 30 days. Location: single rehabilitation centre in Switzerland.
Participants	Eligibility criteria: minimum age 6 years; hospitalised for at least 30 days in a rehabilitation centre in Switzerland; no systemic or inhaled steroids in last 3 months; moderate to severe bronchial obstruction as evidenced by FEV ₁ < 55% predicted at time of entry. Participants who used systemically administered corticosteroids during the trial period were excluded post-randomisation. 50 adults and children (mean age 19.8 years) with CF; 49 completed trial, 25 in intervention group.

Swiss Trial 1996 (Continued)

Interventions	Intervention group: beclomethasone 1500 mcg per day by metered dose inhaler through a spacer device administered either twice or 3x daily. Control group: no treatment.
Outcomes	Lung function tests (FEV ₁ , FVC). Plethysmographic assessment of airway resistance and thoracic gas volume. Single breath carbon monoxide diffusion test.
Notes	Authors contacted: no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details given.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Compared to no treatment so lack of a placebo in the control arm.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participants who used systemically administered corticosteroids during the trial period were excluded post-randomisation.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	No other potential source of bias identified.

Turkish Trial 2017

Study characteristics

Methods	Randomised, placebo controlled trial. Design: parallel. Duration: 8 weeks. Location: single centre (Marmara Hospital) in Turkey.
Participants	Inclusion criteria: aged over 6 years, diagnosed with CF, attending the CF clinic. Participants excluded if taken any form of steroids in last 2 months. 32 participants with CF randomised but 3 excluded so 29 participants included: budesonide group n = 17; placebo group n = 12. Age, mean (SD): budesonide group 11.3 (3.0) years, placebo group 9.5 (2.74) years; whole cohort 10.5 (2.9) years.

Turkish Trial 2017 (Continued)

Gender, number (%): budesonide group 12 (70.6%) males and 5 (29.4%) females; placebo group 8 (66.6%) males and 4 (33.4%) females.

Baseline FEV₁ % predicted, mean (SD): budesonide group 84.83 % predicted (18.16); placebo group 92.94 % predicted (18.18).

Baseline FVC % predicted, mean (SD): budesonide group 81.66 % predicted (15.37); placebo group 87.84 % predicted (18.79).

Pseudomonas colonisation, n (%): budesonide group 8 (47); placebo group 1 (8.3).

Brasfield score, mean (SD): budesonide group 13.31 (6.61); placebo group 12.25 (9.68).

Interventions	Intervention group: 2 mg/day nebulised budesonide. Control group: nebulised 'serum physiologic' 0.9% normal saline.
Outcomes	Lung function (FEV ₁ % predicted, FVC % predicted). Bronchial hyperreactivity (methacholine challenge). Oxidative damage (plasma MDA levels). Inflammation (hsCRP and oxidative burst of monocytes, sputum neutrophils, WBC).
Notes	All of the participants were receiving concomitant nebulised bronchodilator and DNase treatment. Those with Pseudomonas colonisation were also receiving nebulised antibiotics.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	After generating a random number row, participants with even and odd numbers were randomised to receive nebulised budesonide 2 mg/day or 0.9% normal saline.
Allocation concealment (selection bias)	Unclear risk	The person randomising was separate to the one generating the randomisation sequence, but publication only states that the person was blinded to clinical status and does not state whether they had access to the randomisation schedule or not.
Blinding (performance bias and detection bias) All outcomes	High risk	This was a single-blinded study (participants). Chest radiographs and HRCTs were scored by a blinded radiologist.
Incomplete outcome data (attrition bias) All outcomes	Low risk	32 participants were enrolled and randomised. 3 participants were excluded with reasons given: 2 because they were diagnosed and treated for allergic bronchopulmonary aspergillosis and 1 upon parents' request. All were in the placebo group.
Selective reporting (reporting bias)	Low risk	No protocol available but all outcomes listed in the methods were reported in the results.
Other bias	Low risk	No other risks of bias identified.

UK Trial 1996

Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial. Design: parallel. Duration: 2 years. Location: UK.
Participants	36 participants with established CF pulmonary disease. Age range: 16 years to 41 years.
Interventions	Intervention group: fluticasone propionate 500 mcg twice daily via a metered-dose inhaler and spacer. Control group: matching placebo.
Outcomes	Home diary card of symptoms. Domiciliary lung function tests (FEV ₁ , FVC, PEFR using spirometer).
Notes	At 24 months data on FEV ₁ were only available on 8 participants in the fluticasone group and 9 in the placebo group. Authors contacted: no full publication and no further data available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no further details given.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind; fluticasone or matching placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	More than 15% of participants were excluded, but reasons given and numbers equal across groups. At 24 months data on FEV ₁ were only available on 8 participants in the fluticasone group and 9 in the placebo group.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Unclear risk	Trial has never been published in peer-reviewed journals.

UK Trial 1997

Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial.
---------	---

UK Trial 1997 (Continued)

Design: sequence cross-over.

Duration: 6-week treatment period with 4-week washout period then alternative treatment.

Location: UK.

Participants	<p>Eligibility criteria: aged 6 - 17 years, able to perform spirometry reliably, use a Diskhaler and produce sputum.</p> <p>Exclusion criteria: oral or inhaled corticosteroid use in previous 6 months, clinical diagnosis of asthma, use of sodium cromoglycate or beta-2 agonists in previous 6 months, lower respiratory infection requiring antibiotics in previous 3 weeks, CF-related diabetes, portal hypertension, allergic bronchopulmonary aspergillosis, <i>Burkholderia cepacia</i> in sputum.</p> <p>23 children (11 boys) with clinically diagnosed CF randomised.</p> <p>Age, mean (range): 10.3 years (7 years - 17 years).</p> <p>Genotype: 65% homozygous and 30% heterozygous for delta F508.</p>
Interventions	<p>Intervention group: fluticasone propionate by dry powder inhaler in 2 doses equivalent to 400 mcg per day.</p> <p>Control group: matched placebo.</p>
Outcomes	<p>Primary outcome</p> <p>Change from baseline in sputum inflammatory markers (interleukin-8, tumour necrosis factor-α, free neutrophil elastase and neutrophil elastase bound to α1 antiprotease).</p> <p>Covariates: atopic status, disease severity as assessed by FEV₁.</p> <p>Secondary outcome</p> <p>Lung function (FEV₁, FVC).</p> <p>Oxygen saturation.</p> <p>Retrospective symptom score (weekly).</p> <p>Score for well-being and appetite (weekly).</p> <p>Compliance as assessed by unused disks.</p>
Notes	<p>1 participant failed to comply with treatment so the efficacy sample used for analysis consisted of 22 participants.</p> <p>Authors contacted: randomised by sealed envelopes prepared by pharmaceutical company; lung function data provided.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but details of process not discussed; authors confirmed participants randomised in blocks of 4 using sealed envelopes.
Allocation concealment (selection bias)	Low risk	Randomised by sealed envelopes prepared by pharmaceutical company.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, but no details of who exactly was blinded; intervention had a matched placebo.

UK Trial 1997 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 15% of participants were excluded.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Unclear risk	No other potential source of bias identified.

ACTH: adrenocorticotrophic hormone
 CF: cystic fibrosis
 FEF₂₅₋₇₅: forced expiratory flow rate
 FEV₁: forced expiratory volume at 1 second
 FVC: forced vital capacity
 GCP: good clinical practice
 HRCT: high-resolution computer tomography
 hsCRP: high sensitivity C-reactive protein
 mcg: microgram
 MDA: malondialdehyde
P aeruginosa: *Pseudomonas aeruginosa*
 PEF: peak expiratory flow rate
 SD: standard deviation
 SE: standard error
 WBC: white cell count

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Australia Trial 2000	Unable to determine whether treatments were allocated by random or quasi-random methods.
Bessaci 2008	Trial of seretide (which contains an inhaled steroid) plus salmeterol which is not a steroid. Since this trial does not consider an ICS alone, it can not be included.
USA Trial 1996	Not a clinical trial - prospective observational study.
USA Trial 1998	Randomised double-blind trial but in this abstract the outcomes reported were not relevant to those specified in this review.

ICS: inhaled corticosteroid

Characteristics of studies awaiting classification [ordered by study ID]

[Kapustina 2008](#)

Methods	Not clear if study was randomised and if so how.
Participants	40 children with CF (23 females and 17 males) aged 5 to 17.4 years. All participants have "severe" phenotype.
Interventions	Group 1 (14 children): inhaled corticosteroids for mean (SD) 34.29 (37.62) months (minimum 6 months; maximum 120 months). Group 2 (26 children): oral steroids (0.5 mg/kg every other day) for mean (SD) 33.04 (37.98) months (minimum 1 month; maximum 185 months).

Kapustina 2008 (Continued)

All participants received adequate basic therapy including calcium (500 - 1000 mg/day) and vitamin D (200 - 400 IU/day) supplementation.

Outcomes	BMD (g/cm ²) in the lumbar spine.
Notes	Contacted authors for clarification on methods.

BMD: bone mineral density

CF: cystic fibrosis

IU: international units

DATA AND ANALYSES

Comparison 1. Inhaled corticosteroid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mean absolute FEV₁	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1.1 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1.2 At 24 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2 Mean absolute FEV₁	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.1 At 30 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.2 At 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.3 At 6 months pre salbutamol	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.4 At 6 months post salbutamol	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.5 At 12 months pre salbutamol	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.6 At 12 months post salbutamol	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3 Mean absolute FEV₁ (withdrawal study)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3.1 At 2 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3.2 At 4 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3.3 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Change in % predicted FEV₁ post bronchodilator	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4.1 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5 Change in % predicted FEV ₁ (withdrawal study)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5.1 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6 Mean absolute FVC	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.1 At 30 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.2 At eight weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.3 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.4 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7 Mean absolute FVC (withdrawal study)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.1 At 2 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.2 At 4 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.3 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8 Change in % predicted FVC	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8.1 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9 Change in % predicted FVC (withdrawal study)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9.1 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.10 Average patient days in hospital	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.10.1 At 9 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.11 Average patient days on antibiotics	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.11.1 At 9 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.12 Growth velocity	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.13 Growth velocity (withdrawal study)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.13.1 After 8 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 1: Mean absolute FEV₁

Analysis 1.2. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 2: Mean absolute FEV₁

Analysis 1.3. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 3: Mean absolute FEV₁ (withdrawal study)

Analysis 1.4. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 4: Change in % predicted FEV₁ post bronchodilator

Analysis 1.5. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 5: Change in % predicted FEV₁ (withdrawal study)

Analysis 1.6. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 6: Mean absolute FVC

Analysis 1.7. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 7: Mean absolute FVC (withdrawal study)

Analysis 1.8. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 8: Change in % predicted FVC

Analysis 1.9. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 9: Change in % predicted FVC (withdrawal study)

Analysis 1.10. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 10: Average patient days in hospital

Analysis 1.11. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 11: Average patient days on antibiotics

Analysis 1.12. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 12: Growth velocity

Analysis 1.13. Comparison 1: Inhaled corticosteroid versus placebo, Outcome 13: Growth velocity (withdrawal study)

APPENDICES

Appendix 1. Online trials registry searches

Database	Terms	Date searched	Results
World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch)	Title: cystic fibrosis AND Intervention: corticosteroid OR beclomethasone OR budesonide OR fluticasone	04 December 2018	2 records for 2 trials found
ClinicalTrials.gov (www.clinicaltrials.gov)	corticosteroid OR beclomethasone OR budesonide OR fluticasone cystic fibrosis	04 December 2018	9 records for 9 studies found

WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	The Editorial Board of the Cystic Fibrosis and Genetic Disorders Group in discussion with the authors of this review have decided not to continue updating this review due to a lack of new research in this area. If they become of new research in the future, they will re-visit this decision.

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 2000

Date	Event	Description
16 July 2020	Amended	The Editorial Board of the Cystic Fibrosis and Genetic Disorders Group in discussion with the authors of this review have decided not to continue updating this review due to a lack of new research in this area. If they become of new research in the future, they will re-visit this decision.
4 July 2019	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register identified a single additional reference (full paper) to one already included trial (Turkish Trial 2017). Data have been extracted from this paper and entered into the review. A summary of findings table has been added.
4 July 2019	New citation required but conclusions have not changed	A new author (Sherie Smith) has joined the team. Despite the inclusion of some new data, our conclusions remain the same.
22 August 2016	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register did not identify any new references potentially eligible for inclusion in the review.
22 August 2016	New citation required but conclusions have not changed	Since no new data have been added to the review, our conclusions remain the same.
6 October 2014	New citation required but conclusions have not changed	Since we have not been able to include any new information at this update, our conclusions remain the same.
6 October 2014	New search has been performed	A search of the Cystic Fibrosis & Genetic Disorders Review Group's Cystic Fibrosis Trials Register did not identify any new references which were potentially eligible for inclusion in the review. We have updated the plain language summary in light of new guidance.
24 September 2012	New search has been performed	A search of the Cystic Fibrosis & Genetic Disorders Trials Register did not identify any new references for this review.
24 September 2012	New citation required but conclusions have not changed	No new data were added; hence the conclusions of this review have not changed.
6 October 2010	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified four new references to three trials. One of these was an additional reference to an already included trial (Turkish Trial 2017). One trial (two references) was excluded (Bessaci 2008) and one trial is listed as ' Characteristics of studies awaiting classification ' until the authors can clarify the methods used in their study (Kapustina 2008).
26 April 2010	Amended	Contact details updated.
5 November 2008	New search has been performed	The latest searches identified three new references to three studies. One of these references was to a study previously listed as Studies awaiting classification and this study has now been included in the review (CF WISE 2006). The other two new studies

Date	Event	Description
		have both been included (Belgian Trial 2007 ; Turkish Trial 2017); A further study, previously listed as Studies awaiting classification has now been excluded (Australia Trial 2000).
5 November 2008	New citation required and conclusions have changed	The background and discussion sections have been re-drafted; the conclusions and recommendations have been changed. Sarah Walters has stepped down as co-author at this update.
19 June 2008	Amended	Converted to new review format.
24 April 2006	New search has been performed	A search of the Group's Trials Register did not identify any new references for this review. There has been a publication of the CF WISE trial (previously Balfour-Lynn 2001, personal communication – now Balfour-Lynn 2005).
16 May 2005	New search has been performed	The search of the Group's Cystic Fibrosis Trials Register identified one reference, which was subsequently found not to be eligible for inclusion within the review.
19 February 2004	Amended	The lead reviewer is now Dr Ian Balfour-Lynn; Prof Carol Deza-teux remains as a co-reviewer.
19 February 2004	New search has been performed	One further trial has been identified for this updated review (German Trial 1999). This has not altered the conclusions of the earlier review. This update also includes some further information provided from authors of five earlier trials (Canadian Trial 1997 ; Danish Trial 1983 ; Irish Trial 1995 ; UK Trial 1996 , UK Trial 1997). This has allowed methodological quality to be more clearly defined in four trials and has provided data on primary and secondary outcomes as well as study population in three. Data have been entered into the review and are summarised in Data and Analyses (comparison 01, outcomes 05, 06, 07 and 08). Meta-analysis has not been possible reflecting heterogeneity in study design and unavailability of relevant data.

CONTRIBUTIONS OF AUTHORS

Ian Balfour-Lynn contributed to the protocol, identification of trials and co-authored the review and finalised the updates in 2004, 2005 and 2008. Ian Balfour-Lynn acts as guarantor of the review.

Karen Welch contacted authors, extracted and analysed data for the 2008 and 2019 updates.

Sherie Smith extracted and analysed data for the 2019 update and drafted the summary of findings table.

DECLARATIONS OF INTEREST

Ian Balfour-Lynn has no potential conflict of interest.

Karen Welch has no potential conflict of interest.

Sherie Smith has no potential conflict of interest

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In a post hoc change we added 'adrenal insufficiency' to the list of adverse events we planned to investigate.

In line with Cochrane guidance, a summary of findings table was added at the 2019 update. At this time we also re-configured the outcomes relating to pulmonary exacerbations to make the reporting more comprehensive and logical. We have expanded the secondary outcome 'Quality of life' to include symptom scores.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenal Cortex Hormones [administration & dosage] [adverse effects] [*therapeutic use]; Anti-Inflammatory Agents [administration & dosage] [adverse effects] [*therapeutic use]; Cystic Fibrosis [*drug therapy]; Forced Expiratory Volume [drug effects]; Randomized Controlled Trials as Topic; Vital Capacity

MeSH check words

Adolescent; Adult; Child; Humans; Middle Aged; Young Adult