National Institute for Health and Care Excellence

Final

Asthma: diagnosis, monitoring and chronic asthma management

Evidence review: increasing ICS treatment within supported self-management for children and young people

NICE guideline NG80

Evidence review underpinning recommendation 1.10.3 and 1.10.4 in NICE guideline NG80

February 2020

Final

This evidence review was developed by the NICE guideline updates team

November 2024: We published a new collaborative guideline developed jointly by British Thoracic Society (BTS), National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN).

It updates and replaces NICE guideline 80 (published November 2017) and parts of BTS/ SIGN British guideline SIGN 158 (published July 2019).

We have reviewed the evidence and made new recommendations on diagnosis, treatment and monitoring for people with asthma. These recommendations are marked [BTS/NICE/ SIGN 2024].

We have also made some changes without an evidence review. See update information for more details.

See the guideline at www.nice.org.uk/guidance/NG245

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Evidence review: increasing ICS treatment within supported self-management for children and young people

Review question

How effective is an escalation in inhaled corticosteroid (ICS) preventer therapy and is there an optimal increase to prevent asthma exacerbations for children and young people within supported self-management?

Introduction

New evidence indicated that increasing the regular dose of inhaled corticosteroid (ICS) at early signs of loss of asthma control may not reduce the rate of severe asthma exacerbations in children with mild-to-moderate persistent asthma. There was also a suggestion of adverse effects on growth. The NICE guidelines previously recommended that an increased dose of ICS (such as quadrupling) for 7 days should be considered for children and young people who were previously using ICS when asthma control deteriorated. This recommendation was based on extrapolation from several adult studies and 1 study in children and young people of very low quality. This study showed a small non-significant dose response effect. Topic experts advised further studies had been published that showed increased ICS doses for exacerbations in children and young people demonstrated no benefit.

Summary of protocol

Population	• Children and young people with a clinical diagnosis of asthma, using ICS preventer therapy, who are receiving supported self-management including a PAAP (Personalised Asthma Action Plan). • Adults with a clinical diagnosis of asthma, using ICS preventer therapy, who are receiving supported self-management including a PAAP. This data will only be used to extrapolate to children if the committee decide that there is insufficient data for children. Data from adults will be downgraded twice for indirectness. • Setting – primary care and secondary care. • Children and young people (age <18 years) with a clinical diagnosis of asthma
Interventions	Self-initiated increase in the dose of ICS as part of a PAAP at the onset of asthma exacerbations. Interventions will be stratified according to the increase of the ICS dose. ICS doses prescribed will be presented 'as is' and classified as 'low dose', 'moderate dose' or 'high dose' according to NICE's Inhaled corticosteroid doses for NICE's asthma guideline (Table 2: ICS dosages for children aged 5 to 11 years). Furthermore, conversion doses will be

	provided in order to assist making comparisons. Conversion doses will be calculated using available data in the SPCs and BNF.
Comparator	• Keeping the usual maintenance dose of ICS as part of a PAAP at the onset of asthma exacerbations. • Different increases in dose will be kept separate and the evidence will be presented as multiple pairwise comparisons. • Adjustable maintenance dosing (AMD) regimens are not included as they do not look only at how much to increase preventer therapy during exacerbation but also how much to taper it during periods without symptoms.
Outcomes	**Critical outcome:** • Subsequent asthma exacerbations (defined as per study, occurring after index exacerbation requiring treatment as per plan, dichotomous outcome) **Other outcomes:** • Treatment failure (defined as per study, occurring after index exacerbation, requiring treatment as per plan, dichotomous outcome) • Mortality (dichotomous outcome and time to event data) • Quality of life (measured using validated tools such as PAQLQ, AQLQ) (continuous outcome) • School days missed (continuous outcome or possibly dichotomous outcome if looking at children who did versus those who did not) • Parents' workdays missed (continuous outcome or possibly dichotomous outcome if looking at parents who did versus those who did not) • Adult data: workdays missed (continuous outcome or possibly dichotomous outcome if looking at adults who did versus those who did not) • Asthma control (measured using validated tools such as C-ACT, ACT, ACQ or SGRQ) (continuous outcome) • Hospital admissions (dichotomous outcome and rate data) • Reliever/rescue medication use (continuous outcome) • Lung function (such as change in FEV1 or PEF) (continuous outcome). • Oxygen saturation • Adverse events: ○ linear growth (continuous outcome), ○ infections (all respiratory – dichotomous outcome), ○ infections (serious respiratory (including pneumonia and TB – dichotomous outcome), ○ adrenal insufficiency (as defined by study, including abnormal short synacthen test and morning cortisol – dichotomous outcome)

Methods and process

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

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

The Minimally Important Differences (MIDs) used are provided in Appendix B.

Effectiveness evidence

After removing duplicates, 1,677 references were screened on their titles and abstracts. 145 studies were obtained and reviewed against the inclusion criteria as described in the review protocol (Appendix A).

Included studies

Overall,5 parallel RCTs were included (see Appendix E for evidence tables).

Excluded studies

140 references were excluded because they did not meet the eligibility criteria (see Appendix K for the excluded studies).

Percentage agreement between the two reviewers

The percentage agreement between the two reviewers was 100%.

Summary of studies included in the effectiveness evidence

Reference	Population	PAAP?	Usual ICS and increased ICS arms	Outcomes	Limitations
Child studies					
Jackson 2018 Parallel RCT USA	Recruitment: 5 to 11 years Mean age 8.0 years (SD 1.9)	Yes	Usual ICS: fluticasone, moderate paediatric dose. If exacerbation, moderate dose for 7 days. Increased ICS: fluticasone, moderate paediatric dose. If exacerbation, above maximum licenced threshold for 7 days.	Subsequent asthma exacerbations Treatment failure Adverse events Hospital admissions Reliever/rescue medication use Lung function	The asthma control test measured severity of attack for those who experienced an attack. It did not measure asthma control for all participants. Increased dose group 2.2 times dose of upper limit of maximum for children.
Adult studies					
Foresi 2000 Parallel RCT Italy	Recruitment: 18 to 65 years Mean age 39.4 years (SD 14.5)	Yes	Usual ICS: budesonide, low dose. If exacerbation, placebo for 7 days. Increased ICS: budesonide low dose. If exacerbation, moderate dose for 7 days.	Subsequent asthma exacerbations Adverse events	Does not say how many participants dropped out of each arm. No details regarding the methods of randomisation. No details regarding the blinding of staff. This study involves a PAAP but is an adult study.
Harrison 2004 Parallel RCT UK	Recruitment: ≥16 years Mean age 49.0 years (SD 13.5)	Yes	Usual ICS: low to high doses of ICSs. If loss of control, placebo. Increased ICS: low to high doses of ICSs. If loss of control, 2x usual low to high dose of ICS.	Subsequent asthma exacerbations Lung function	We do not know what ICS(s) were given or their exact doses. Increased dose group 2 times dose of upper limit of maximum for adults. This is an adult study.
McKeever 2018	Recruitment: ≥16 years	Yes	Usual ICS: moderate doses of ICSs. If loss of control: bronchodilator.	Subsequent asthma exacerbations	This study was not blinded. This study involves a PAAP but is an adult study. The

Reference	Population	PAAP?	Usual ICS and increased ICS arms	Outcomes	Limitations
Parallel RCT UK	Mean 57 years (SD 15)		Increased ICS: moderate doses of ICSs. If loss of control: bronchodilator + high to above maximum licenced threshold until symptoms or peak flow have returned to normal or after a maximum of 14 days.	Treatment failure Adverse events Quality of life Lung function	interquartile range of the dose for the increased dose group spans a mid-high to 2x maximum high dose for adults.
Oborne 2016 Parallel RCT UK	Recruitment: 16 years and older Mean age 54.0 years (SD 13.5)	Yes	Usual ICS: beclometasone, low to moderate dose. If there was deterioration, participants took a placebo. Increased ICS: beclometasone, low to moderate dose. If there was a deterioration, participants doubled their dose for 7 days. This is equivalent to an adult low dose to a high dose.	Subsequent asthma exacerbations Adverse events	This study involves a PAAP but is an adult study

See Appendix D for full evidence tables.

Summary of the effectiveness evidence

Outcomes that favoured the usual ICS dose

These outcomes only have adult data.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Adults: Adverse events: Number of participants who experienced an adverse event (values greater than 1 favour usual ICS dose)					
3 (Foresi 2000, McKeever 2018, Oborne 2009)	Parallel RCTs	2866	RR 1.73 (1.16, 2.57)	Very low	Favours usual ICS dose
Adults: Treatment failure: Participants who withdrew consent, had poor adherence or withdrew due to lack of efficacy (values greater than 1 favour usual ICS dose)					
2 (McKeever 2018, Oborne 2009)	Parallel RCTs	3320	RR 1.86 (1.29, 2.68)	Very low	Favours usual ICS dose
Key: RR = risk ratio					

Outcomes that favoured the increased ICS dose

These outcomes only have adult data.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Adults: Subsequent asthma exacerbations: Number of participants experiencing at least 1 severe asthma exacerbation during the study period (values greater than 1 favour usual ICS dose)					
4 (Foresi 2000, Harrison 2004, McKeever 2018, Oborne 2009)	Parallel RCTs	2766	RR 0.85 (0.78, 0.93)	Very low	Favours increased ICS dose
Adults: Quality of life: Mini Asthma Quality of Life Questionnaire (scores range from 1 to 7, higher values indicating better quality of life) (values greater than 0 favour increased ICS dose)					
1 (McKeever 2018)	Parallel RCT	499	MD 0.30 (0.08, 0.52)	Very low	Favours increased ICS dose
Adults: Adverse events: Rate ratio of hospital admissions (values greater than 1 favour usual ICS dose)					
1 (McKeever 2018)	Parallel RCT	1871	RR 0.17 (0.05, 0.57)	Very low	Favours increased ICS dose
Adults: Lung function: Mean area under the curve of the peak expiratory flow (PEF) (values greater than 0 favour increased ICS dose)					
1 (McKeever 2018)	Parallel RCT	529	MD 36.00 (10.23, 61.77)	Very low	Favours increased ICS dose
Key: MD = mean difference; RR = risk ratio					

Outcomes that were not statistically significant

Outcomes for children are given first, followed by outcomes for adults.

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Children: Subsequent asthma exacerbations: Number of participants experiencing at least 1 severe asthma exacerbation during the study period (values greater than 1 favour usual ICS dose)					
1 (Jackson 2018)	Parallel RCT	192	RR 1.32 (0.90, 1.94)	Very low	Cannot differentiate between groups
Children: Treatment failure: participants who withdrew consent, had poor adherence and withdrew due to lack of efficacy (values greater than 1 favour usual ICS dose)					
1 (Jackson 2018)	Parallel RCT	254	RR 1.30 (0.59, 2.86)	Very low	Cannot differentiate between groups
Children: Reliever medication use: Number of salbutamol inhalations per day from 7 days before to 14 days after the onset of yellow-zone alerts (values above 0 favour usual ICS dose)					
1 (Jackson 2018)	Parallel RCT	192	MD 2.00 (-1.91, 5.91)	Low	Cannot differentiate between groups
Children: Lung function: The percentage of days with Peak Expiratory Flows (PEFs) <80% of their reference value during the exacerbation period (yellow time zone) (values greater than 0 favour increased ICS dose)					
1 (Jackson 2018)	Parallel RCT	192	MD -3.00 (-13.26, 7.26)	Very low	Cannot differentiate between groups
Children: Adverse events: Relative incidence rate of hospital admissions (incidents per year) (values greater than 1 favour usual ICS dose)					
1 (Jackson 2018)	Parallel RCT	192	RIR 9.04 (0.48, 170.91)	Low	Cannot differentiate between groups
Children: Adverse events: Relative incidence rate of emergency department visits, urgent care visits, or unscheduled health care consultations per year (values greater than 1 favour usual ICS dose)					
1 (Jackson 2018)	Parallel RCT	192	RIR 0.17 (-0.17, 0.51)	Low	Cannot differentiate between groups
Children: Adverse events: Relative rate of linear growth: centimetres per year (values greater than 1 favour increased ICS dose)					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 (Jackson 2018)	Parallel RCTs	192	MD -0.22 (-0.46, 0.02)	Low	Cannot differentiate between groups
Adults: Lung function: Maximum fall in Peak Expiratory Flow (PEF) recorded at any time during the study, litres per minute (values greater than 0 favour usual ICS dose)					
1 (Harrison 2004)	Parallel RCT	353	MD -10.00 (-20.90, 0.90)	Very low	Cannot differentiate between groups
Adults: Adverse events: Number of participants who experienced a serious adverse event (values greater than 1 favour usual ICS dose)					
1 (McKeever 2018)	Parallel RCT	1871	RR 0.50 (0.25, 1.03)	Very low	Cannot differentiate between groups
Adults: Adverse events: Mortality (values greater than favour)					
1 (McKeever 2018)	Parallel RCT	1871	RR 3.02 (0.12, 73.94)	Very low	No difference between groups
Adults: Adverse events: Relative incidence rate of emergency department visits, urgent care visits, or unscheduled health care consultations per year (values greater than 1 favour usual ICS dose)					
1 (McKeever 2018)	Parallel RCT	1871	MD -0.11 (-0.22, 0.00)	Very low	Cannot differentiate between groups
Adults: Adverse events: Number of participants who experienced pharyngitis and/or laryngitis (values greater than 1 favour usual ICS dose)					
2 (Foresi 2000, Oborne 2009)	Parallel RCTs	545	RR 1.09 (0.19, 6.29)	Very low	Cannot differentiate between groups
Adults: Adverse events: Number of participants who experienced an upper respiratory tract infection (values greater than 1 favour usual ICS dose)					
1 (Oborne 2009)	Parallel RCT	403	RR 3.14 (0.13, 76.53)	Very low	Cannot differentiate between groups

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Adults: Adverse events: Number of participants who experienced a lower respiratory tract infection (including pneumonia) (values greater than 1 favour usual ICS dose)					
1 (McKeever 2018)	Parallel RCT	1871	RR 0.84 (0.26, 2.74)	Very low	Cannot differentiate between groups
Adults: Adverse events: Number of participants who experienced sinusitis (values greater than 1 favour usual ICS dose)					
1 (Oborne 2009)	Parallel RCT	403	RR 0.35 (0.01, 8.50)	Very low	Cannot differentiate between groups
Key: RR = risk ratio; MD = mean difference					

See Appendix G for the full GRADE tables.

Economic evidence

A total of 124 potentially relevant studies was returned by the economic literature search (see Appendix C). Of these, 123 could be confidently excluded based on title and abstract, leaving 1 that met eligibility criteria when reviewed in full text.

Included studies

The included study is summarised in an evidence profile, below; a full evidence table is provided in Appendix I.

Evidence statement

One partially applicable within-RCT cost–utility analysis was included (McKeever et al 2018) with potentially serious limitations in adults with asthma compared two self-management plans: 1 including quadrupling of inhaled corticosteroids when poorly controlled and 1 without dose-escalation. It found that quadrupling dose was associated with lower costs and more QALYs; however, at a 95% confidence level, the data were consistent with no difference in either costs or QALYs. In probabilistic analysis, the chance that quadrupling dose is associated with an ICER of £20,000/QALY or better was 94%.

Excluded studies

No studies were excluded at full-text review.

Summary of included cost effectiveness evidence

Study	Limitations	Applicability	Other comments	Incremental (dose escalation -v- none)			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
McKeever et al. (2018) Self-management plan indicating quadrupling of normal ICS dose when poorly managed versus self-management plan without ICS modification	Potentially serious	Partially applicable	Within-RCT cost–utility analysis, collecting resource-use and quality of life (EQ-5D) data	-24 (-122 to 71)	0.02 (-0.0 to 0.04)	Dominant	94% chance dose-escalation is cost effective if QALYs are valued at £20K each (86% in complete cases only)

Economic model

No original economic modelling was undertaken for this review.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The most important outcome was subsequent asthma exacerbations. This is because it directly measures the outcome of interest. In an ideal world, the next most important tier of outcomes would be symptoms as measured by validated asthma control measurement tools, quality of life and mortality. Included with quality of life are school days missed and parent's workdays missed. However, the committee agreed that mortality should not feature as a consideration in this review because the frequency of expected deaths is so small that all studies are underpowered to measure it.

The outcomes above matter most to children, young people, parents and healthcare professionals. They are commonly discussed during routine consultations to enable decisions to be made as to whether therapy should be continued, augmented or reduced.

Adverse events are the next important, particularly long-term harmful effects. They matter to children, parents and clinicians. However, the data for linear growth was non-significant.

Reliever medication use is a less direct measurement compared to asthma exacerbations. For the purposes of this review, "treatment failure" refers to the number of participants who did not complete a study through non-adherence or through withdrawing from the study. It does not include those who were lost to follow up. It not a useful outcome because non-adherence is difficult to measure unless expensive adherence monitoring is in place.

The committee agreed that lung function tests do not appear to be as important for children as they are for adults. Although lung function is frequently assessed in asthma clinical trials because it is an objective evaluation of efficacy, parents and clinicians place much more emphasis on clinical measures of asthma control when assessing the effectiveness of therapy. The committee agreed that if we were reviewing evidence for children being managed in an emergency department setting, lung function might play a more significant role. This is because in the context of a moderate or worse exacerbation, FEV1 and PEF are generally low and remain low for quite a while. However, the children and young people in the studies in this review were experiencing milder asthma. The general literature and committee experience suggest that in these circumstances, FEV1 and PEF fluctuate. Furthermore, FEV1 and PEF are largely affected by bronchodilators, not ICS.

No study measured oxygen saturation in this review. Had they measured this, it would be less useful than lung function. This is because oxygen saturation is affected by lung function and other variables, such as metabolism, degree of skin contact with the pulse oximeter and quality of the pulse oximeter.

The quality of the evidence

When the protocol was written, it was decided that only RCTs should be reviewed because the committee was aware of one RCT on the topic of interest (Jackson 2018). In case of insufficient evidence, the committee were willing to review RCTs where there was an

increase in the dose of ICS at the onset of worsening asthma that was not self-initiated. This is because the committee expected that the effectiveness of ICS would be similar in self-initiated studies and non-self-initiated studies because both involve using ICS to treat symptoms. However non self-initiated studies were not included in this review. The committee agreed that observational studies would not be of high enough quality to address this issue because of selection bias and confounding.

Adult RCTs that otherwise matched the inclusion criteria were also reviewed. This was to enable the committee to review data on adolescent populations within these studies if it existed. The committee was alert to the possibility that child and adult study data could differ from each other. For example, it was interested to know if the data might show an age range where a transition point existed.

The child study

The child study was very low-quality evidence. Jackson 2018 is partially direct evidence because the increased ICS dose exceeded the maximum upper limit for a paediatric high dose by 2.2 times as specified by NICE and the BNF. For the most important outcome, subsequent asthma exacerbations, the 95% confidence interval crossed both ends of the defined minimally important difference (MID) interval.

The adult studies

The 4 adult studies included participants who had a weighted mean age of 55 years (SD 15 years). Therefore, the proportion of adolescents in these studies is too small to extrapolate this data to adolescents with asthma: There are groups of adults with asthma who have steroid-resistant phenotypes. Some adult asthma is related to obesity and these people tend not to respond to steroids.

Research recommendations

A self-initiated quadrupling of the dose of maintenance ICS when asthma worsens has been a common treatment to reduce the chances of exacerbations occurring. However, this is based on data of very low quality. The committee agreed that data is needed from large pragmatic RCTs.

Benefits and harms

No recommendation for changing ICS dose if asthma control worsens

The committee agreed there is not enough evidence to recommend increasing the regular ICS dose in a personalised asthma plan if asthma control deteriorates. Conversely, the evidence is too poor to warrant a ‘do not do’ recommendation.

The data suggest that increasing the ICS dose does not result in any benefits or harms compared to the usual ICS dose. This finding is consistent with the committee’s experience with regards to most children. The data was nearly statistically significant in favour of the usual ICS dose for linear growth compared to the increased ICS dose. However, the committee’s a priori level of concern was a statistically significant difference. Furthermore, Jackson 2018 used an increased ICS dose that exceeded the maximum upper limit recommended in the UK for a paediatric high dose by 2.2 times.

Rather than write a ‘do not prescribe an increased ICS dose’ recommendation, the committee decided to have no recommendation for the following reasons:

- In the committee's experience, an increased ICS dose controls the asthma of some children. Some children stumble across the finding that an increased ICS dose manages their asthma. Children feel reassured if they are told they may adjust their dose because an increased dose works for some children. However, clinicians should not routinely advise children to increase their ICS dose because this will not work for most children
- Self-managing children feel it is reassuring to have control over their dose of ICS.
- Many self-managing children are used to adjusting their ICS dose. If they were to be told to reduce their dose to a set level, they would feel uncomfortable. For example, the lay members on the committee advised that they found it useful to regulate their ICS dose at the time of exacerbations. There is no evidence to justify vetoing this practice: To do so would disregard their clearly expressed experience.

(As a point of clarification, the adjustments to ICS dose mentioned in the bullet-points above refer to the short-term increase with ICS alone in response to deterioration, not to the variable ICS/long-acting beta agonist dose used in the maintenance and reliver therapy regimen.)

The committee decided against writing a 'do not routinely offer' recommendation. It agreed that this implied that there was an identifiable characteristic of some children that suggested they would benefit from an increased ICS dose, and the committee did not think this was the case.

Recommendation to review the self-management plan if the child has asthma that is not responding to their personalised action plan

The committee noted a void in the guideline about what to do if asthma symptoms worsen. Therefore, the committee drafted a recommendation advising children to request a review of their self-management plan. This new recommendation was a consensus statement with the benefits of improving the safety and quality of life of children. There are no potential harms.

The context behind the need for this recommendation is that a study from the Nuffield Trust and the Association for Young People's Health found in an analysis of 19 high-income countries that death rates for asthma in 10 to 24-year-olds was highest in the UK among all 14 European nations included. A national review of asthma deaths in the UK showed that most child asthma deaths involve children who have frequent but mild symptoms that are not responding to their personalised action plan.

This recommendation represents best clinical practice that should normally be occurring but usually does not. Children who have milder but reoccurring symptoms who are not responding to their personalised action plan usually do not have their self-management plan reviewed because until now there has been no recommendation to do so. The committee agreed that many children live with mild and frequent symptoms. These children are usually the ones who are most at risk of dying because of an exacerbation. Children and parents often feel unsure as to when the child should have their self-management programme reviewed. The new recommendation addresses these issues and children should feel more in control of their asthma.

If symptoms are mild but reoccurring, the self-management programme should be reviewed. This is because asthma reviews only occur annually. There may be wider issues that need addressing before the annual review date, such as poor inhaler technique, the prescribing of a different inhaler and changing factors in the child's environment that may be precipitating reoccurring mild symptoms and/or poor asthma control.

The committee agreed that many self-managing children with asthma are non-adherent with regards to taking their regular ICS. However, it is impossible for clinicians to know which children are non-adherent. Therefore, this is another reason for children to have their asthma self-management plan reviewed if they are not responding to their personalised action plan; self-management programs include education. This is a necessary recommendation because in primary care, few children are routinely monitored.

Finally, it is unsatisfactory for children to be self-managing poorly controlled asthma using ever-increasing ICS maintenance doses which has little effect.

Cost effectiveness and resource use

Only 1 published economic analysis was available to inform the committee; however, this related to adults only, and its outcomes were subject to substantial uncertainty. Therefore, the committee concluded that it would be unsafe to extrapolate from this evidence to the paediatric setting.

The committee agreed that, in general terms, ICS are inexpensive and exacerbations are potentially costly. As a result, committee members had no doubt that, if increasing dose could be shown to prevent exacerbations, the small extra outlay on ICS would almost certainly represent a good use of NHS resources. However, as the evidence does not demonstrate that increased dosage has this effect in children, such an approach could not be recommended as a routine part of asthma management plans. Nevertheless, as noted above, the committee had experience that some children are comfortable modulating their ICS dose in response to symptoms and appear to derive benefit from doing so. If it can be assumed that this behaviour prevents even a small number of exacerbations, the relatively small cost of additional ICS would not be a reason to discourage it.

Similarly, the committee agreed that the resource-use inherent in reviewing the self-management programmes of children whose asthma is poorly controlled is likely to be offset by reductions in future exacerbation events. This would have benefits for the child in question and also lead to cost-savings in the NHS.

Other factors the committee took into account

The committee agreed that the recommendations are feasible. They should be acceptable to children, families and healthcare professionals.

Some families are less structured in their use of healthcare and resources. Therefore, ensuring there is sufficient guidance from the self-management programme review and personalised asthma plan should go some way to addressing this.

Resource impact

The recommendations made by the committee based on this review are not expected to have a substantial impact on resources.

References – included studies

Effectiveness

Foresi, A; Morelli, M C; Catena, E (2000) Low-dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. On behalf of the Italian Study Group. Chest 117(2): 440-6

Harrison, T W, Oborne, J, Newton, S et al. (2004) Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. Lancet (London, England) 363(9405): 271-5

Jackson, Daniel J, Bacharier, Leonard B, Mauger, David T et al. (2018) Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations. The New England journal of medicine 378(10): 891-901

McKeever, Tricia, Mortimer, Kevin, Wilson, Andrew et al. (2018) Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations. The New England journal of medicine 378(10): 902-910

Oborne, Janet, Mortimer, Kevin, Hubbard, Richard B et al. (2009) Quadrupling the dose of inhaled corticosteroid to prevent asthma exacerbations: a randomized, double-blind, placebo-controlled, parallel-group clinical trial. American journal of respiratory and critical care medicine 180(7): 598-602

Further studies cited in the discussion of the evidence section

Nuffield Trust (Shah R, Hagell A, Cheung R) International comparisons of health and wellbeing in adolescence and early adulthood. Page 43

Appendices

Appendix A – Review protocol

Review protocol for the inhaled corticosteroid maintenance dose for children with poorly controlled asthma

How effective is an escalation in ICS preventer therapy and is there an optimal increase to prevent asthma exacerbations for children and young people within supported self-management?

ID	Field	Content
0.	PROSPERO registration number	CRD42019146485
1.	Review title	How effective is an escalation in ICS preventer therapy and is there an optimal increase to prevent asthma exacerbations for children and young people within supported self-management?
2.	Review question	How effective is an escalation in ICS preventer therapy and is there an optimal increase to prevent asthma exacerbations for children and young people within supported self-management?
3.	Objective	To determine whether there is an optimal increase in ICS preventer therapy to prevent asthma exacerbations for children and young people within supported self-management
4.	Searches	Sources to be searched Clinical searches - Medline, Medline in Process, Medline EPub Ahead of Print, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records).

ID	Field	Content
		Economic searches - Medline, Medline in Process, Medline EPub Ahead of Print, Embase, Econlit, NHS EED (legacy records) with economic evaluations and quality of life filters applied. Supplementary search techniques • None identified Limits • Studies reported in English • Study design RCT and SR filter was applied (as agreed) Animal studies were excluded from the search results • Conference abstracts were excluded from the search results • No date limit was set.
5.	Condition or domain being studied	Asthma in children
6.	Population	• Children and young people with a clinical diagnosis of asthma, using ICS preventer therapy, who are receiving supported self-management including a PAAP (Personalised Asthma Action Plan). • Adults with a clinical diagnosis of asthma, using ICS preventer therapy, who are receiving supported self-management including a PAAP. This data will only be used to extrapolate to children if the committee decide that there is insufficient data for children. Data from adults will be downgraded twice for indirectness. (We included adult studies that included a PAAP

ID	Field	Content
		and would have included any child non-PAAP studies. However, we excluded adult non-PAAP studies.) • Setting – primary care and secondary care. • Population age: <18 years
7.	Intervention/Exposure/Test	Self-initiated increase in the dose of ICS as part of a PAAP at the onset of asthma exacerbations. Interventions will be stratified according to the increase of the ICS dose. ICS doses prescribed will be presented 'as is' and classified as 'low dose', 'moderate dose' or 'high dose' according to NICE's Inhaled corticosteroid doses for NICE's asthma guideline (Table 2: ICS dosages for children aged 5 to 11 years). Furthermore, conversion doses will be provided in order to assist making comparisons. Conversion doses will be calculated using available data in the SPCs and BNF. If the evidence is insufficient: An increase in the dose of ICS at the onset of asthma exacerbations that is not self-initiated. We will then downgrade for indirectness.
8.	Comparator/Reference standard/Confounding factors	• Keeping the usual maintenance dose of ICS as part of a PAAP at the onset of asthma exacerbations.

ID	Field	Content
		• Different increases in dose will be kept separate and the evidence will be presented as multiple pairwise comparisons. • Adjustable maintenance dosing (AMD) regimens are not included as they do not look only at how much to increase preventer therapy during exacerbation but also how much to taper it during periods without symptoms.
9.	Types of study to be included	RCT and Systematic review of RCTs • Minimum duration of studies should be 3 months in order to allow for a reasonable proportion of participants to have experienced an exacerbation requiring the use of their PAAP.
10.	Other exclusion criteria	• If the committee feel that the data for children is sufficient, we will exclude the data for adults. • Non-English language studies. • Non-randomised studies/observational studies. • Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.

ID	Field	Content
		• Studies where the only comparator arm has LABA: In the UK, LABA cannot be prescribed for asthma without ICS. Therefore, a control arm with LABA without ICS would not be a valid comparison. We will include studies that compare different doses of ICS in combination with a dose of LABA that is the same in each arm. • Studies where there has been a change in dose of other controller medications, such as LABA and/or LTRA. • Studies where there are different doses of reliever/rescue medication(s) for the different arms of the study, such as for SABA and/or OCS.
11.	Context	Children who are continuing to have poorly controlled asthma despite using their usual maintenance dose of inhaled corticosteroids. This review is to revise guideline NG80.
12.	Primary outcomes (critical outcomes)	• Subsequent asthma exacerbations (defined as per study, occurring after index exacerbation requiring treatment as per plan, dichotomous outcome)
13.	Secondary outcomes (important outcomes)	• Treatment failure (defined as per study, occurring after index exacerbation, requiring treatment as per plan, dichotomous outcome) • Mortality (dichotomous outcome and time to event data) • Quality of life (measured using validated tools such as PAQLQ, AQLQ) (continuous outcome) • School days missed (continuous outcome or possibly dichotomous outcome if looking at children who did versus those who did not)

ID	Field	Content
		• Parents' workdays missed (continuous outcome or possibly dichotomous outcome if looking at parents who did versus those who did not) • Adult data: workdays missed (continuous outcome or possibly dichotomous outcome if looking at adults who did versus those who did not) • Asthma control (measured using validated tools such as C-ACT, ACT, ACQ or SGRQ) (continuous outcome) • Hospital admissions (dichotomous outcome and rate data) • Reliever/rescue medication use (continuous outcome) • Lung function (such as change in FEV1 or PEF) (continuous outcome). • Oxygen saturation • Adverse events: o linear growth (continuous outcome), o infections (all respiratory – dichotomous outcome), o infections (serious respiratory (including pneumonia and TB – dichotomous outcome),

ID	Field	Content
		o adrenal insufficiency (as defined by study, including abnormal short synacthen test and morning cortisol – dichotomous outcome)
14.	Data extraction (selection and coding)	10% of the abstracts will be reviewed by two reviewers. Any disagreement will be resolved by discussion or, if necessary, a third independent reviewer. If there is a disagreement between the reviewers, a further 10% of the abstracts will be reviewed by two reviewers, with this process continuing until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Any disagreement will be resolved by discussion or, if necessary, a third independent reviewer. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. In other words, the Cochrane Risk of Bias tool, RoB 2.0 for parallel RCTs was used.
16.	Strategy for data synthesis	The strategy used for data synthesis is described in Appendix B.
17.	Analysis of sub-groups	Data for children and adults will appear as separate subgroups on the same meta-analyses: We need to assess whether the evidence for children is sufficient. The subject of this review is children and data for adults should be more indirect. There will be further subgroup analyses if there is heterogeneity within the two subgroups above:

ID	Field	Content
		• Further age stratification • Current smokers versus ex- or non-smokers • Children who live in homes where smoking occurs versus children who live in smoke-free homes • Children who live in areas where there is a higher level of pollution versus children who live in areas where there is a lower level of pollution • ICS dose prior to increase (low versus high) • Primary versus secondary care
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)

ID	Field	Content		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	29/07/2019		
22.	Anticipated completion date	09/10/2019		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑

ID	Field	Content		
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	**5a. Named contact** Centre for Guidelines National Institute for Health and Care Excellence 10 Spring Gardens | London SW1A 2BU | United Kingdom **5b Named contact e-mail** asthma@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and Centre for Guidelines		
25.	Review team members	From the Centre for Guidelines: • Technical lead: Caroline Mulvihill		

ID	Field	Content
		• Technical analyst: Toby Mercer • Health economist: Gabriel Rogers • Information specialist: Elizabeth Barrett • Project manager: Anneka Patel
26.	Funding sources/sponsor	F
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPEROFILES/146485_STRATEGY_20190808.pdf

ID	Field	Content
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Children, asthma, inhaled corticosteroid, ICS, dose, worsening
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☒ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued

ID	Field	Content
35..	Additional information	
36.	Details of final publication	www.nice.org.uk

Appendix B – Methods

Screening

All abstracts were screened.

Incorporating published systematic reviews

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

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs were quality assessed using the Cochrane Risk of Bias Tool version 2. Each individual study was classified into one of the following three groups:

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

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

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

Methods for combining intervention evidence

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

Data for children, adults and adolescents (within the adult studies) was to be presented as separate subgroups within the same meta-analyses. However, no data for adolescents within the adult studies was found.

Relative risks were calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and incidence rate ratios were calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by

applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses are less heterogeneous (with $I^2 < 50\%$) the results from these subgroups will be reported using fixed effects models.

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

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

Minimal clinically important differences (MIDs)

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

MIDs found through this process and used to assess imprecision in the guideline are given in **Table 1**. For other continuous outcomes not specified in the table below, no MID was defined.

1

2 **Table 1: Identified MIDs**

Outcome	MID	Source	Assessment
Mortality	RR 0.9 to 1.111	Houchen-Wolloff L., Evans R. A. Unravelling the mystery of the 'minimum important difference' using practical outcome measures in chronic respiratory disease. Chronic Respiratory Disease. 2019 16:1-11	As discussed in Houchen-Wolloff 2019, the clinical importance of mortality is intuitive. Therefore, the committee agreed that a relative risk MID of 0.9 to 1.111 sounded reasonable: It is important to take statistically significant differences in mortality seriously. Furthermore, the baseline mortality rate for children who have asthma is small. Therefore, a relatively small MID of 10% seemed appropriate.
Hospitalisations	RR 0.9 to 1.111	Houchen-Wolloff L., Evans R. A. Unravelling the mystery of the 'minimum important difference' using practical outcome measures in chronic respiratory disease. Chronic Respiratory Disease. 2019 16:1-11	As discussed in Houchen-Wolloff 2019, the clinical importance of frequency of serious events is intuitive. Therefore, the committee agreed that a relative risk MID of 0.9 to 1.111 sounded reasonable: It is important to take statistically significant differences in hospitalisations seriously. Therefore, this relatively small MID of 10% seemed appropriate.
Paediatric Asthma Quality of Life Questionnaire (PAQLQ) (1 to 7 scale)	MD 0.42	Juniper EF, Guyatt GH, Feeny D, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. Quality of Life Research. 1996 5:35–46	In a study of 52 children with asthma, mean age 12 years (SD 3.1), those considered to have experienced a minimal important improvement (global rating scale change of ±2 or ±3 on a scale of +7 to -7) had a mean PAQLA scale change of 0.42 on a scale of 1 to 7. The committee agreed with this MID of 0.42 because a global rating scale change of ±2 or ±3 represent changes of 'a little better/worse' and 'somewhat better/worse' respectively as described in: Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol. 1994 Jan;47(1):81-7

Outcome	MID	Source	Assessment
Asthma Control Questionnaire for children – UK wording (0 to 6 scale)	MD 0.5	Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. Eur Respir J. 2010 Dec;36(6):1410-6.	In a study of 35 children with asthma, mean age 10.4 years (SD 2.6), those considered to have experienced a minimal important improvement (global rating scale change of ±2 or ±3 on a scale of +7 to -7) had a mean ACQ scale (UK wording) change of 0.5 on a scale of 0 to 6. The committee agreed with this MID of 0.5 because a global rating scale change of ±2 or ±3 represent changes of 'a little better/worse' and 'somewhat better/worse' respectively as described in: Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol. 1994 Jan;47(1):81-7
Asthma Control Questionnaire for children – US wording (0 to 6 scale)	MD 0.42	Nguyen JM, Holbrook JT, Wei CY, Gerald LB, Teague WG, Wise RA; American Lung Association Asthma Clinical Research Centers. Validation and psychometric properties of the Asthma Control Questionnaire among children. J Allergy Clin Immunol. 2014 Jan;133(1):91-7.e1-6.	In a study of 305 children with asthma, mean age 11 years (SD 3), those considered to have experienced a minimal important difference (an episode of poor asthma control determined by anchoring the ACQ scale to the Asthma Control Test's MID of 3 points) had a mean ACQ scale (US wording) change of 0.42 on a scale of 0 to 6. The committee accepted this anchor-based method in favour of the distribution-based method that was also presented in this study.
Childhood Asthma Control Test (C-ACT) (0 to 27 scale)	MD 2	Bime C, Gerald JK, Wei CY, Holbrook JT, Teague WG, Wise RA, Gerald LB. Measurement characteristics of the childhood Asthma-Control Test and a shortened, child-only version. NPJ Prim Care Respir Med. 2016 Oct 20;26:16075.	In a study of 161 children with asthma, mean age 9 years (SD 1.6), a MID of 2 was calculated because this is 0.5 of the SD, which was 4.1. The committee accepted this distribution-based MID because an anchor-based MID was unavailable.
Childhood Asthma Control Test child responses (C-ACTc) (0 to 12 scale)	MD 1	Bime C, Gerald JK, Wei CY, Holbrook JT, Teague WG, Wise RA, Gerald LB. Measurement characteristics of the childhood Asthma-Control Test and a shortened, child-only version. NPJ Prim Care Respir Med. 2016 Oct 20;26:16075.	In a study of 161 children with asthma, mean age 9 years (SD 1.6), a MID of 1 was calculated because this is 0.5 of the SD, which was 2. The committee accepted this distribution-based MID because an anchor-based MID was unavailable.

Outcome	MID	Source	Assessment
Asthma Control Test (ACT) (5 to 25 scale)	MD 3	Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. J Allergy Clin Immunol. 2009 Oct;124(4):719-23.e1.	In four samples that had a total of 4118 adults, anchor-based methods assessed the relationship of differences in ACT scores to worsening of asthma. Predictive analyses showed that a difference of 3 points on the ACT was associated with a subsequent 76% increased risk (95% CI: 73% to 79%) of excess short-acting b-agonist use and a 33% increased risk (95% CI: 31% to 35%) of exacerbations. The committee accepted this anchor-based method in favour of the distribution-based method that was also presented in this study.
Asthma Control Questionnaire for adults (0 to 6 scale)	MD 0.5	Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. 2005 May;99(5):553-8.	In a study of 552 adults with asthma, the MID of all 4 versions was close to 0.5 because this is close to the standard errors. The committee accepted this distribution-based MID because an anchor-based MID was unavailable.
Asthma Quality of Life Questionnaire (0 to 6 scale)	MD 0.5	Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol. 1994 Jan;47(1):81-7.	In a study of 39 adults with asthma, those considered to have experienced a minimal important improvement (global rating scale change of ±2 or ±3 on a scale of +7 to -7) had a mean AQLQ scale change of 0.5 on a scale of 0 to 6. The committee agreed with this MID of 0.5 because a global rating scale change of ±2 or ±3 represent changes of 'a little better/worse' and 'somewhat better/worse' respectively.
Mini Asthma Quality of Life Questionnaire (0 to 6 scale)	MD 0.5	Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J. 1999 Jul;14(1):32-8.	In a study of 40 adults with asthma, all participants received the MiniAQLQ and the ACQ. Both are 0 to 6 scales. The MID of the ACQ was already established to be 0.5 and this established the anchoring of the MiniAQLQ MID as 0.5.
Forced expiratory volume in 1 second (FEV1)	MD 0.23L	Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma	In a study of 86 adults with asthma (mean age 35 years), an improvement of FEV1 by 0.23 L was the minimal perceivable improvement. Child MID data could not be

Outcome	MID	Source	Assessment
		measures in a clinical trial? Eur Respir J. 1999 Jul;14(1):23-7.	found. Therefore, the committee agreed that if we included child studies having FEV1 data, we should adjust this MID according to the coefficient of variation for age published in: Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, Rosenthal M, Corey M, Lebecque P, Cole TJ. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med. 2008 Feb 1;177(3):253-60. Epub 2007 Nov 15.
Peak expiratory flow (PEF)	MD 18.79 L/min	Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? Eur Respir J. 1999 Jul;14(1):23-7.	In a study of 86 adults with asthma (mean age 35 years), an improvement of PEF by 18.79 L/min was the minimal perceivable improvement. Child MID data could not be found. Therefore, the committee agreed that if we included child studies having PEF data, we should adjust this MID according to the coefficient of variation for age published in: Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, Rosenthal M, Corey M, Lebecque P, Cole TJ. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med. 2008 Feb 1;177(3):253-60. Epub 2007 Nov 15.

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For continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For continuous outcomes expressed as a standardised mean difference where no other MID was available, an MID of 0.5 was used. For relative risks where no other MID was available, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review makes explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all randomised controlled trials was initially rated as high quality and data from observations studies were originally rated as low quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in **Table 2**.

Table 2: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study.

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

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

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

Summary of evidence

The evidence is presented in the form of a table because the committee agreed in advance that effect sizes would be an important consideration. Summary of evidence is stratified by comparison and reflects evidence that was statistically significant.

Where the data are only consistent, at a 95% confidence level, with an effect in one direction, and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect. In all other cases, we state that the evidence could not differentiate between the comparators.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in **Table 3**.

Table 3 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in **Table 4**.

Table 4 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

The searches were run on 6th August 2019. The following databases were searched: Medline, Medline in Process, Medline epub ahead of print, Embase (all via the Ovid platform), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews (all via the Wiley platform) and the Database of Abstracts of Reviews of Effect (via the Centre for Reviews and Dissemination platform). The McMaster balanced RCT filters and health-evidence.ca Systematic Review filters were used in Medline and Embase databases. MHRA drug safety alerts were searched on 8th August 2019.

The Medline strategy is presented below. It was translated for other databases.

1 exp Asthma/

2 asthma*.ti.

3 1 or 2

4 self care/ or self administration/ or self-management/

5 ((self-manage* or self-monitor* or self-care or self-administer* or self-initiate* or self manage* or self monitor* or self care or self administer* or self initiate*) adj4 (strateg* or program* or guide* or information or educat* or plan* or paap or pap or diary or diaries or tool* or booklet* or manual* or pamphlet* or leaflet* or review*)).ti,ab.

6 ((supported or patient* or individualis* or individualiz*) adj4 (self-manage* or self manage* or self-care or self care or self-monitor* or self monitor* or self- initiate* or self initiate* or self-administer* or self administer* or plan* or paap or pap)).ti,ab.

7 ((patient* or individualis* or individualiz*) adj4 (diary or diaries or program* or tool* or educat*)).ti,ab. (

8 (dose* adj5 (doubl* or tripl* or trebl* or quadrupl* or quintupl* or exacerbat* or maintenance* or maintain* or prevent* or reliev*)).ti,ab.

9 or/4-8

10 (inhaled corticosteroid* or inhaled glucocorticoid* or ics).ti,ab.

11 triamcinolone/

12 budesonide/

13 beclomethasone/

14 fluticasone/ (

15 formoterol fumarate/

16 Budesonide Formoterol Drug Combination/

17 Mometasone Furoate/

18 Albuterol/

19 Salmeterol Xinafoate/

20 (budesonide or beclomethasone* or beclometasone* or ciclesonide or fluticasone* or flunisolide or triamcinolone or pulmicort or qvar or formoterol or fostair or alvesco or mometasone* or asmanex or aerobid or symbicort or "clenil modulite mdi" or RINN or flixotide or seretide or aerospan or "BDP-HFA" or oxis or atimos or NEXThaler or fobumix or albuterol or proventil or salbutamol or sultanol or ventolin or salmeterol).ti,ab.

21 or/10-20

22 9 and 21

23 3 and 22

24 randomized controlled trial.pt.

25 randomi?ed.mp.

26 placebo.mp.

27 or/24-26

28 (MEDLINE or pubmed).tw.

29 systematic review.tw.

30 systematic review.pt.

31 meta-analysis.pt.

32 intervention$.ti.

33 or/28-32

34 27 or 33

35 23 and 34

36 limit 35 to english language

Searches to identify economic evidence were run on 7th August 2019 in Medline, Medline in Process, Medline epub ahead of print, Embase and Econlit (all via the Ovid platform) and the Health Technology Assessment Database (via the Centre for Reviews and Dissemination platform). These searches were date limited to the date of the previous guideline search(12th September 2016). NICE inhouse economic evaluation and quality of life filters were applied to lines 1 to 23 of the above strategy in the Medline and Embase databases.

The Medline version of the filters are presented below

Economic evaluations

1. Economics/ (27062)
2. exp "Costs and Cost Analysis"/
3. Economics, Dental/
4. exp Economics, Hospital/
5. exp Economics, Medical/

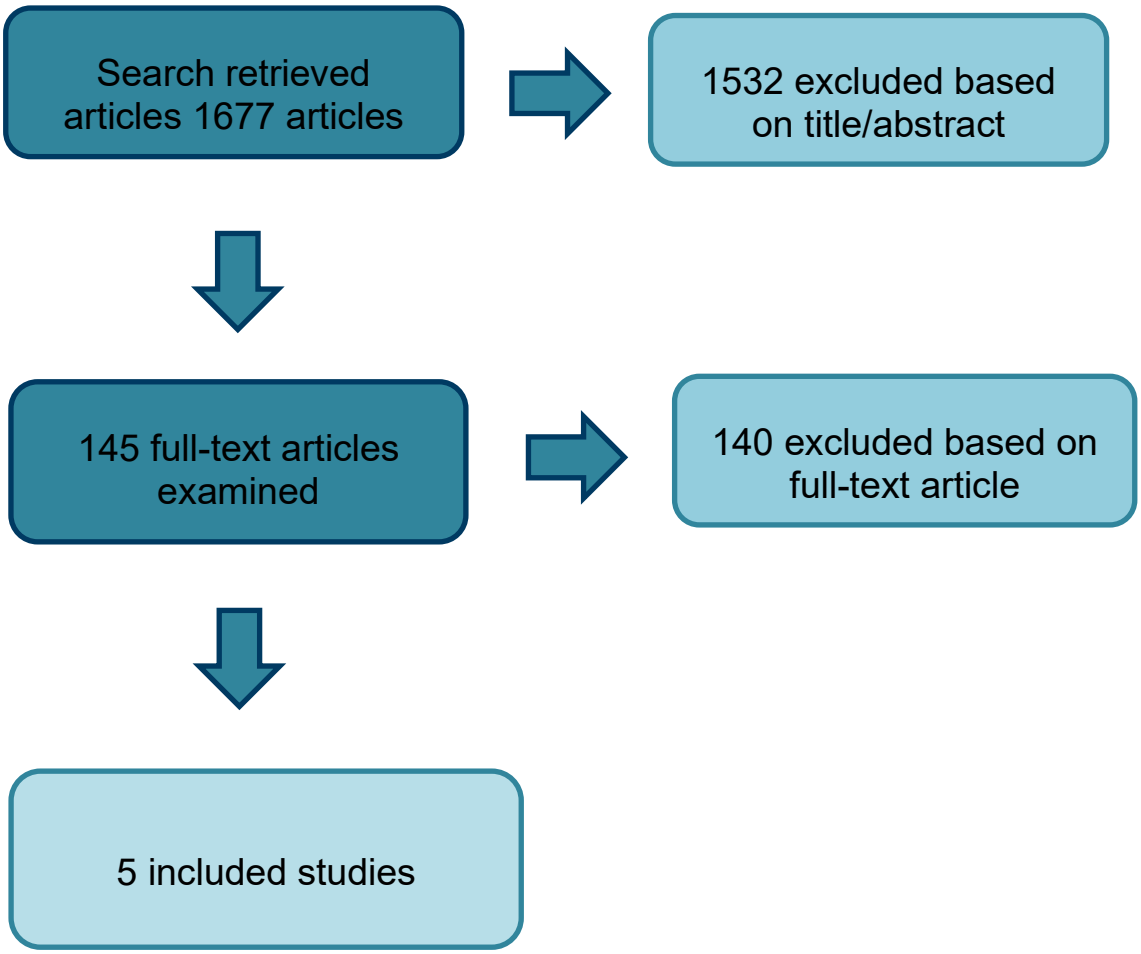
6. Economics, Nursing/
7. Economics, Pharmaceutical/
8. Budgets/
9. exp Models, Economic/
10. Markov Chains/
11. Monte Carlo Method/
12. Decision Trees/
13. econom$.tw.
14. cba.tw.
15. cea.tw.
16. cua.tw.
17. markov$.tw.
18. (monte adj carlo).tw.
19. (decision adj3 (tree$ or analys$)).tw.
20. (cost or costs or costing$ or costly or costed).tw.
21. (price$ or pricing$).tw.
22. budget$.tw.
23. expenditure$.tw.)
24. (value adj3 (money or monetary)).tw.)
25. (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26. or/1-25

Quality of Life

1. "Quality of Life"/
2. quality of life.tw.
3. "Value of Life"/
4. Quality-Adjusted Life Years/
5. quality adjusted life.tw.
6. (qaly$ or qald$ or qale$ or qtime$).tw.
7. disability adjusted life.tw. (
8. daly$.tw.
9. Health Status Indicators/
10. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15. (euroqol or euro qol or eq5d or eq 5d).tw.
16. (qol or hql or hqol or hrqol).tw.
17. (hye or hyes).tw.
18. health$ year$ equivalent$.tw.
19. utilit$.tw.
20. (hui or hui1 or hui2 or hui3).tw.
21. disutili$.tw.
22. rosser.tw.

23. quality of wellbeing.tw.
24. quality of well-being.tw.
25. qwb.tw.
26. willingness to pay.tw.
27. standard gamble$.tw.
28. time trade off.tw.
29. time tradeoff.tw.
30. tto.tw.
31. or/1-30

Appendix D – Effectiveness evidence study selection



Appendix E – Effectiveness evidence

Effectiveness studies

Foresi, 2000

Foresi, 2000

Bibliographic Reference	Foresi, A; Morelli, M C; Catena, E; Low-dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. On behalf of the Italian Study Group.; Chest; 2000; vol. 117 (no. 2); 440-6

Study details

Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	Outpatient clinics
Study dates	Not provided. This study was received for publication in 1999
Duration of follow-up	6 months
Sources of funding	This study was supported by a grant from Astra Farmaceutici, S.p.A., Italy
Inclusion criteria	Essential for this review: Participants had a clinical diagnosis of asthma

	All patients had documented histories of asthma as defined by the American Thoracic Society. Baseline FEV1 50% or greater and 90% or less of predicted values. Presence of wheeze, cough, chest tightness, shortness of breath at rest that interfered with normal daily activity during a 2-week pre-study observation period Optional for this review: Participants included adults 18 to 65 years of age Participants were using ICS preventer therapy Patients followed an established treatment with inhaled beclomethasone dipropionate (500 to 1000 micrograms daily) for at least 4 weeks
Exclusion criteria	Use of systemic corticosteroids Including oral steroids On a high dose of ICS On a high dose of beclomethasone dipropionate (1000 micrograms daily)) Participants who have seasonal asthma Participants who are current smokers Participants who are ex-smokers
Sample size	142
Split between study groups	Usual ICS: 75 Increased ICS: 67
Loss to follow-up	10 participants overall. Does not say from which arms

% Female	Usual ICS: 47% Increased ICS: 58%
Mean age (SD)	Usual ICS: 39.8 years (15.4) Increased ICS: 39.0 years (13.5)
Run-in period details	Following the 2-week prestudy observation period, all eligible patients entered a 4-week prestudy treatment period during which they were asked to inhale 800 micrograms of budesonide. Participants were then randomised to receive treatments.
The definition of poor asthma control that prompted the study drug to be given in the PAAP	Throughout the study period, the patients kept a daily record of respiratory symptoms (wheeze, cough, chest tightness, and shortness of breath), number of asthmatic exacerbations, morning and evening PEF values, and daily use of additional treatments. Exacerbation of asthma was defined by a fall in PEF <70% from baseline value, calculated during the last 2-week prestudy treatment period on at least 2 consecutive days. In case of an exacerbation, patients were instructed to start with the inhaled additional randomized treatment for 7 days (either placebo or budesonide 200 mg qid). If PEF remained <70% of baseline value for 2 additional consecutive days, the patients were advised to follow a short course treatment of oral steroids (prednisolone 30 mg for 3 to 10 days, as judged by the investigators) to restore clinical condition and lung function (PEF >70% of baseline).
Definition of an asthma exacerbation used to measure the main outcome	As above. (Poor control was the same thing as an exacerbation in this study)
Outcome measures	Subsequent asthma exacerbations Adverse events

Study arms

	Usual ICS: budesonide 200 micrograms daily (equivalent to 200 micrograms of beclometasone, which is the lower limit of a low dose (NICE)) + if loss of control: placebo for 7 days (N = 64) **Increased ICS: usual ICS + if loss of control: budesonide 800 micrograms daily for 7 days (equivalent to 1000 micrograms of beclometasone, which is the upper limit of a moderate dose (NICE)) (N = 55)**

Domain 1: Bias arising from the randomisation process

1. 1. Was the allocation sequence random?

Probably yes

(No details regarding the methods of randomisation)

1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?

Probably yes

1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?

No

Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

2.1. Were participants aware of their assigned intervention during the trial?

Probably no

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

Probably no

(No details regarding the blinding of staff)

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?

No/Probably no

2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?

N/A

2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?

N/A

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?

Yes

2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?

N/A

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

(No details regarding the blinding of staff)

Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

2.1. Were participants aware of their assigned intervention during the trial?

Probably no

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

Probably no

(No details regarding the blinding of staff)

2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?

Probably yes

2.4. Could failures in implementing the intervention have affected the outcome?

Probably yes

2.5. Did study participants adhere to the assigned intervention regimen?

Yes

2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?

Yes

Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)

Low

Domain 3. Bias due to missing outcome data

3.1 Were data for this outcome available for all, or nearly all, participants randomised?

Yes

3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?

N/A

3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?

N/A

3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?

N/A

3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?

N/A

Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

4.1 Was the method of measuring the outcome inappropriate?

Yes

4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?

No

4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?

No

4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?

Probably no

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?

N/A

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?

Yes

5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?

No/Probably no

5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?

No/Probably no

Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

High

(Does not say how many participants dropped out of each arm. No details regarding the methods of randomisation. Taking oral corticosteroids for an asthma exacerbation should not influence bias because this was the same treatment for both usual and increased ICS arms. Furthermore, use of oral corticosteroids is a normal treatment for exacerbations.)

Overall Directness

Indirectly applicable because it is an adult study

Harrison, 2004

Harrison, 2004

Bibliographic Reference	Harrison, T W; Oborne, J; Newton, S; Tattersfield, A E; Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial.; Lancet (London, England); 2004; vol. 363 (no. 9405); 271-5

Study details

Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Hospital outpatients
Study dates	Not provided. This study was published in 2004
Duration of follow-up	12 months
Sources of funding	NHS Executive
Inclusion criteria	Essential for this review: Participants had a clinical diagnosis of asthma Optional for this review: Participants included adults Participants were aged 16 years or older Participants were using ICS preventer therapy At least 1 asthma exacerbation Participants had to have taken a course of oral corticosteroids or doubled their dose of ICS temporarily in the previous 12 months to treat or prevent an asthma exacerbation.
Exclusion criteria	Participants who are current smokers

	Smoking more than 10 pack-years Participants who are ex-smokers Smoking more than 10 pack-years Recent unstable asthma During the 2-week run-in period
Sample size	353
Split between study groups	Usual ICS: 178 Increased ICS: 175
Loss to follow-up	Usual ICS: 11 Increased ICS: 10
% Female	Usual ICS: 71% Increased ICS: 64%
Mean age (SD)	Usual ICS: 48 years (14) Increased ICS: 50 years (13)
Run-in period details	There was a 2-week run-in period where participants recorded baseline symptom scores
The definition of poor asthma control that	There was a PAAP. If participants asthma control worsened, they were instructed to take the additional inhaler that either had placebo or another dose of their usual ICS. This would double the dose. The doubled dose persisted for 14 days.

prompted the study drug to be given in the PAAP	Worsened control was defined as morning PEF falling by 15% or if their symptom score increased by 1 point. Symptom score was on a 4-point scale: 0 = no symptoms; 3 = incapacitating symptoms. Participants were given a 10-day course of prednisolone (30 mg daily) to be taken if their asthma control deteriorated to the point that they would normally take oral corticosteroids or if their PEF fell by 40% from the mean run-in value.
Definition of an asthma exacerbation used to measure the main outcome	The primary end point was the number of participants who needed oral prednisolone in each group
Outcome measures	Subsequent asthma exacerbations Lung function

Study arms

	Usual ICS: low to high doses of ICS. Exact ICS(s) and their doses were unspecified. A maximum high dose is equivalent to 2000 micrograms of beclometasone daily (NICE). If loss of control: placebo (N = 178) **Increased ICS: usual ICS. If loss of control: 2x usual low to high dose of ICS. A 2x maximum high dose is equivalent to 4000 micrograms of beclometasone daily (NICE) (N = 175)**

Domain 1: Bias arising from the randomisation process

1. 1. Was the allocation sequence random?

Yes

1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?

No information

1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?

No

Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

2.1. Were participants aware of their assigned intervention during the trial?

No

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

No information

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?

No/Probably no

2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?

N/A

2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?

N/A

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?

Yes

2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?

N/A

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

2.1. Were participants aware of their assigned intervention during the trial?

No

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

No information

2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?

Probably yes

2.4. Could failures in implementing the intervention have affected the outcome?

No information

2.5. Did study participants adhere to the assigned intervention regimen?

Yes

2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?

N/A

Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)

Low

Domain 3. Bias due to missing outcome data

3.1 Were data for this outcome available for all, or nearly all, participants randomised?

Yes

3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?

N/A

3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?

N/A

3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?

N/A

3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?

N/A

Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

4.1 Was the method of measuring the outcome inappropriate?

No

4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?

No

4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?

No information

4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?

Probably no

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?

N/A

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?

Yes

5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?

No/Probably no

5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?

No/Probably no

Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Indirectly applicable

(We do not know what ICS(s) were given – not all have licences for use in the UK. Increased dose group 2 times dose of upper limit of maximum for adults. This is an adult study)

Jackson, 2018

Jackson, 2018

Bibliographic Reference	Jackson, Daniel J; Bacharier, Leonard B; Mauger, David T; Boehmer, Susan; Beigelman, Avraham; Chmiel, James F; Fitzpatrick, Anne M; Gaffin, Jonathan M; Morgan, Wayne J; Peters, Stephen P; Phipatanakul, Wanda; Sheehan, William J; Cabana, Michael D; Holguin, Fernando; Martinez, Fernando D; Pongracic, Jacqueline A; Baxi, Sachin N; Benson, Mindy; Blake, Kathryn; Covar, Ronina; Gentile, Deborah A; Israel, Elliot; Krishnan, Jerry A; Kumar, Harsha V; Lang, Jason E; Lazarus, Stephen C; Lima, John J; Long, Dayna; Ly, Ngoc; Marbin, Jyothi; Moy, James N; Myers, Ross E; Olin, J Tod; Raissy, Hengameh H; Robison, Rachel G; Ross, Kristie; Sorkness, Christine A; Lemanske, Robert F Jr; National Heart, Lung, and Blood Institute AsthmaNet; Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations.; The New England journal of medicine; 2018; vol. 378 (no. 10); 891-901

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Departments of paediatrics
Study dates	2014 to 2016
Duration of follow-up	Usual ICS: mean follow-up 42.5 weeks

	Increased ICS: mean follow-up 40.3 weeks
Sources of funding	National Heart, Lung, and Blood Institute. Many authors received fees from pharmaceutical companies for serving on advisory boards
Inclusion criteria	Essential for this review: Participants had a clinical diagnosis of asthma Participants had doctor-diagnosed asthma and a history of at least one asthma exacerbation treated with systemic glucocorticoids in the previous year. Eligible participants were required to have one of the following: mild-to-moderate persistent asthma treated with step 2 therapy according to the National Asthma Education and Prevention Program Expert Panel Report (EPR) 3 (steps range from 1 to 6, with step 6 therapy being used in patients with the most severe disease); current symptoms or an exacerbation history that qualified the child for step 2 therapy; or current treatment with step 3 therapy according to the EPR 3 and a score on the Childhood Asthma Control Test (C-ACT) of more than 19 (on a scale from 0 to 27, with higher scores indicating greater asthma control; minimal clinically important difference, 2.0). Preferred for this review: Participants included children 5 to 11 years of age Participants were using ICS preventer therapy
Exclusion criteria	Asthma symptoms that are too severe At enrolment, no more than two prednisone treated exacerbations in the past 6 months, >5 exacerbations in the previous year that had been treated with systemic glucocorticoids or a history of life-threatening asthma A forced expiratory volume in 1 second (FEV1) that is too low Under 80% of the predicted value Unwilling to change their old treatment regimen for the new study treatment regimen >25% non-adherent to treatment during the 4-week run-in period
Sample size	192

Split between study groups	Usual ICS: 98 Increased ICS: 94
Loss to follow-up	Usual ICS: 13 Increased ICS: 12
% Female	Usual ICS: 36% Increased ICS: 35%
Mean age (SD)	Usual ICS: 7.9 years (1.9) Increased ICS: 8.1 years (1.8)
Run-in period details	Participants were entered into a 4-week run-in period to establish adherence of more than 75% to the use of open-label trial medication (fluticasone propionate at a dose of 44 µg per inhalation, two inhalations twice daily), daily completion of an electronic diary, and asthma control (C-ACT score >19) at the randomization visit. All the participants continued to receive open-label low-dose therapy as maintenance (“green zone”) therapy throughout the 52-week trial.
The definition of poor asthma control that prompted the study drug to be given in the PAAP	Participants were randomly assigned in a 1:1 ratio to receive blinded therapy either at the low dose or at the high dose (fluticasone at a dose of 220 µg per inhalation, two inhalations twice daily) for 7 days at the early signs of loss of asthma control. The green-zone low-dose inhaler (fluticasone propionate at a dose of 44 µg per inhalation, two inhalations twice daily), was discontinued while the blinded yellow-zone inhaler was used; thus, the low-dose group continued to receive the same dose of inhaled glucocorticoids throughout the trial. Yellow-zone episodes were identified by the occurrence of any of the following: the use of two doses (four inhalations) of rescue albuterol in 6 hours, the use of three doses (six inhalations) of rescue albuterol in 24 hours, or one night awakening that was due to asthma that was treated with albuterol.
Definition of an asthma	A PAAP was used. Therefore, this is described in the section above

exacerbation used to measure the main outcome	
Outcome measures	Subsequent asthma exacerbations The primary outcome was the rate of severe asthma exacerbations treated with systemic glucocorticoids during the blinded treatment period. Systemic glucocorticoids were started after consultation with a trial clinician according to previously published criteria: the use of more than 6 inhalations of albuterol in 6 hours, the use of 12 or more inhalations of albuterol in 24 hours, night awakenings leading to albuterol use during 2 of 3 consecutive nights, or the use of 8 or more inhalations of albuterol during 2 of 3 consecutive days. Treatment failure Adverse events Hospital admissions Reliever/rescue medication use Lung function

Study arms

	Usual ICS: fluticasone 176 micrograms daily or if loss of control: fluticasone 176 micrograms daily (both equivalent to 352 micrograms of beclometasone daily, which is a moderate paediatric dose (SPC & NICE)) (N = 98) **Increased ICS: fluticasone 176 micrograms daily or if loss of control: fluticasone 880 micrograms daily (equivalent to 1,760 micrograms of beclomethasone daily), which exceeds the maximum upper limit for a paediatric high dose by 2.2 times, for 7 days (SPC & NICE) (N = 94)**

Domain 1: Bias arising from the randomisation process

1. 1. Was the allocation sequence random?

No information

(No details of the method of randomisation provided in the separate protocol document either)

1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?

No information

1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?

No

Risk of bias judgement for the randomisation process

Some concerns

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

2.1. Were participants aware of their assigned intervention during the trial?

Probably no

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

Probably no

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?

No/Probably no

2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?

N/A

2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?

N/A

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?

Yes

2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?

N/A

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

2.1. Were participants aware of their assigned intervention during the trial?

Probably no

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

Probably no

2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?

Probably yes

2.4. Could failures in implementing the intervention have affected the outcome?

Probably yes

2.5. Did study participants adhere to the assigned intervention regimen?

Yes

2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?

N/A

Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)

Low

Domain 3. Bias due to missing outcome data

3.1 Were data for this outcome available for all, or nearly all, participants randomised?

No

(Data was not in an extractable format for treatment failure and adverse events)

3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?

No information

3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?

Yes

(Lack of adverse events could result in no data reported)

3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?

No

3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?

Yes

Risk-of-bias judgement for missing outcome data

Some concerns

Domain 4. Bias in measurement of the outcome

4.1 Was the method of measuring the outcome inappropriate?

Probably yes

(The asthma control test measured severity of attack for those who experienced an attack. It did not measure asthma control for all participants.)

4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?

No

4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?

Probably no

4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?

N/A

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?

N/A

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?

Yes

5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?

No/Probably no

5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?

No/Probably no

Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Moderate risk

(The asthma control test measured severity of attack for those who experienced an attack. It did not measure asthma control for all participants.)

Overall Directness

Partially applicable

(The increased dose of fluticasone exceeds the maximum upper dose limit for a paediatric high dose by 2.2 times. Although this study excluded participants who were >25% non-adherent, we did not downgrade for indirectness because this was done equally for both study arms.)

McKeever, 2018

McKeever, 2018

Bibliographic Reference	McKeever, Tricia; Mortimer, Kevin; Wilson, Andrew; Walker, Samantha; Brightling, Christopher; Skeggs, Andrew; Pavord, Ian; Price, David; Duley, Lelia; Thomas, Mike; Bradshaw, Lucy; Higgins, Bernard; Haydock, Rebecca; Mitchell, Eleanor; Devereux, Graham; Harrison, Timothy; Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations.; The New England journal of medicine; 2018; vol. 378 (no. 10); 902-910

Study details

Study type	Randomised controlled trial (RCT)

Study location	UK
Study setting	80% of participants were recruited from primary care and 20% from secondary care
Study dates	2013 to 2017
Duration of follow-up	12 months
Sources of funding	Health Technology Assessment Programme of the National Institute for Health Research
Inclusion criteria	Essential for this review: Participants had a clinical diagnosis of asthma Participants had experienced one or more asthma exacerbations in the last 12 months requiring treatment with systemic corticosteroids Optional for this review: Participants included children and adults Men or women aged ≥16 years Participants were using ICS preventer therapy Participants had been prescribed a licensed dose of inhaled corticosteroid. In other words, steps 2–4 of the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines Smokers could be included Current smokers could be included provided that the recruiting centres had good evidence of underlying asthma (i.e. a life-long history of asthma, a >12% forced expiratory volume in 1 second (FEV1) reversibility, or sputum or blood eosinophilia)
Exclusion criteria	Asthma symptoms that are too severe On maintenance systemic corticosteroids (i.e. step 5 of the BTS/SIGN guidelines) Likely chronic obstructive pulmonary disease (COPD)

	A history more in keeping with smoking-related chronic obstructive pulmonary disease (in other words, smoked >20 pack-years, without evidence of significant reversibility or blood eosinophilia) Using a combination inhaler for both maintenance and relief treatment Experienced an exacerbation between randomisation and study treatment Participants who are pregnant Participants who are breastfeeding Participants who are planning to become pregnant
Sample size	1,871
Split between study groups	Usual ICS: 938 Increased ICS: 933
Loss to follow-up	Usual ICS: 25 Increased ICS: 21
% Female	Usual ICS: 67% Increased ICS: 69%
Mean age (SD)	Usual ICS: 56.7 years (15.2) Increased ICS: 56.2 years (15.5)
Run-in period details	There was no special run-in period: Participants took their usual medication for asthma

The definition of poor asthma control that prompted the study drug to be given in the PAAP	The investigators compared two self-management plans that were based on a plan developed by Asthma UK and used in the United Kingdom at the time of trial design. The plans were identical other than zone 2 of the plans. Zone 1 described well-controlled asthma and recommended continuation of current treatment. Zone 2 described deteriorating asthma control and recommended increased bronchodilator medication and an increase in the dose of inhaled glucocorticoids by a factor of 4 (quadrupling group) or increased bronchodilator medication alone (non-quadrupling group). Zones 3 and 4 described the development of an exacerbation and when to start oral glucocorticoids and seek medical intervention (zone 3) and what to do in the event of a life-threatening exacerbation (zone 4). Participants were sent an automated text message every month to remind them to follow their self-management plan. Additional glucocorticoid inhalers that were required to achieve a quadrupling of the dose were provided free of charge.
Definition of an asthma exacerbation used to measure the main outcome	A PAAP was used. Therefore, this is described in the section above
Outcome measures	Subsequent asthma exacerbations Treatment failure Adverse events Adverse events and serious adverse events relating to established adverse effects of inhaled glucocorticoids were reported during the 14 days after activation of zone 2 of the self-management plan. After a request from the data monitoring committee, cases of pneumonia were reported for up to 4 weeks after activation of zone 2. Quality of life Change in score on the Mini Asthma Quality of Life Questionnaire: Mini-AQLQ; scores range from 1 to 7, with higher values indicating better quality of life; minimal important difference: 0.5. Lung function The area under the curve of the morning peak expiratory flow 2 weeks after activation of zone 2 of the self-management plan.

Study arms

	Usual ICS: median equivalent dose of beclometasone 800 micrograms per day, IQR 400 to 1000, which is a moderate adult dose (NICE) (N = 938)
	Increased ICS: usual dose of ICS or if loss of control: bronchodilator + median equivalent dose of beclometasone 3,200 micrograms per day, IQR 1,600 to 4,000) until symptoms or peak flow have returned to normal or after a maximum of 14 days. The IQR spans a mid-high to 2x maximum high dose for adults (NICE) (N = 933)

Domain 1: Bias arising from the randomisation process

1. 1. Was the allocation sequence random?

Yes

1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?

No

(There was no blinding)

1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?

No

Risk of bias judgement for the randomisation process

High

(There was no blinding)

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

2.1. Were participants aware of their assigned intervention during the trial?

Yes

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

Yes

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?

No/Probably no

2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?

N/A

2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?

N/A

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?

Yes

2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?

N/A

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

2.1. Were participants aware of their assigned intervention during the trial?

Yes

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

Yes

2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?

Yes

2.4. Could failures in implementing the intervention have affected the outcome?

N/A

2.5. Did study participants adhere to the assigned intervention regimen?

Yes

2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?

Yes

Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)

Low

Domain 3. Bias due to missing outcome data

3.1 Were data for this outcome available for all, or nearly all, participants randomised?

Yes

3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?

Yes

3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?

Not applicable

3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?

Not applicable

3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?

Not applicable

Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

4.1 Was the method of measuring the outcome inappropriate?

No

4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?

No

4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?

Yes

4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?

Probably no

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?

Probably no

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?

Yes

5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?

No/Probably no

5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?

No/Probably no

Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

High

(This study was not blinded)

Overall Directness

Indirectly applicable

(UK study but the IQR of the dose range for the increased dose group spans a mid-high to 2x maximum high dose for adults. This is an adult study.)

Oborne, 2009

Oborne, 2009

Bibliographic Reference	Oborne, Janet; Mortimer, Kevin; Hubbard, Richard B; Tattersfield, Anne E; Harrison, Tim W; Quadrupling the dose of inhaled corticosteroid to prevent asthma exacerbations: a randomized, double-blind, placebo-controlled, parallel-group clinical trial.; American journal of respiratory and critical care medicine; 2009; vol. 180 (no. 7); 598-602

Study details

Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	General practices recruited but the setting is unclear
Study dates	2004 to 2007
Duration of follow-up	12 months
Sources of funding	Asthma UK
Inclusion criteria	Essential for this review: Participants had a clinical diagnosis of asthma Worsening asthma symptoms in the previous 12 months but not in the preceding 4 weeks. Likewise for oral corticosteroids. To be randomized the lowest morning peak flow in the run-in period had to be greater than 90% of the mean peak flow over the run-in period. Optional for this review: Participants included adults Aged 16 years and older Participants were using ICS preventer therapy beclometasone 200 to 1000 micrograms daily, which is an adult low dose to moderate dose (NICE)
Exclusion criteria	Asthma symptoms that are too severe On a maintenance dose of oral corticosteroids Participants who are pregnant

	Participants who are breastfeeding Participants who have had a recent illness Clinically significant illness Participants who are current smokers Smoked more than 20 pack-years Participants who are ex-smokers Smoked more than 20 pack-years
Sample size	400
Split between study groups	Usual ICS: 203 Increased ICS: 197
Loss to follow-up	Usual ICS: 3 Increased ICS: 0
% Female	Usual ICS: 63% Increased ICS: 59%
Mean age (SD)	Usual ICS: 55 years (13) Increased ICS: 53 years (14)
Run-in period details	Participants had to complete a 2-week run-in period recording morning PEF using a mini-Wright PEF meter as the best of three measurements.

The definition of poor asthma control that prompted the study drug to be given in the PAAP	This was a PAAP. Randomized participants received an individualized asthma management plan and either an active or placebo corticosteroid inhaler. The management plan instructed participants to record their morning PEF if they believed their asthma control was deteriorating or they. developed symptoms of an upper respiratory tract infection and to start using the study inhaler if PEF fell by 15% or more on 2 consecutive days, or 30% on 1 day, from the mean morning PEF measured during the run-in period. The study inhaler was to be taken for 7 days in addition to participants' normal asthma treatment and a daily diary of morning PEF was to be completed. The study inhaler and PEF diary were continued for a further 7 days if morning PEF had not returned to the prestudy baseline value after the initial 7 days. Participants were also instructed to commence oral prednisolone 30 mg daily if their asthma deteriorated to a point where they would normally start systemic corticosteroids, if their general practitioner advised them to do so or, as a safety precaution, if their PEF fell by 40% or more from baseline.
Definition of an asthma exacerbation used to measure the main outcome	The primary outcome was exacerbations of asthma treated with oral corticosteroids.
Outcome measures	Subsequent asthma exacerbations Adverse events

Study arms

	Usual ICS: beclometasone 200 to 1000 micrograms daily, which is an adult low dose to moderate dose (NICE). If there was deterioration, participants took a placebo (N = 203)
	Increased ICS: beclometasone 200 to 1000 micrograms daily, which is an adult low dose to moderate dose (NICE). If there was a deterioration, participants doubled their dose for 7 days. This is equivalent to an adult low dose to a high dose (NICE) (N = 197)

Domain 1: Bias arising from the randomisation process

1. 1. Was the allocation sequence random?

Yes

1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?

Yes

1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?

No

Risk of bias judgement for the randomisation process

Low

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

2.1. Were participants aware of their assigned intervention during the trial?

No

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

No

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?

N/A

2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?

N/A

2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?

N/A

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?

Yes

2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?

N/A

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Low

Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

2.1. Were participants aware of their assigned intervention during the trial?

No

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

No

2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?

N/A

2.4. Could failures in implementing the intervention have affected the outcome?

Probably yes

2.5. Did study participants adhere to the assigned intervention regimen?

Yes

2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?

N/A

Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)

Low

Domain 3. Bias due to missing outcome data

3.1 Were data for this outcome available for all, or nearly all, participants randomised?

Yes

3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?

Probably yes

3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?

Probably no

3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?

N/A

3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?

N/A

Risk-of-bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

4.1 Was the method of measuring the outcome inappropriate?

Yes

4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?

No

4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?

N/A

4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?

N/A

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?

N/A

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?

Yes

5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?

No/Probably no

5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?

No/Probably no

Risk-of-bias judgement for selection of the reported result

Low

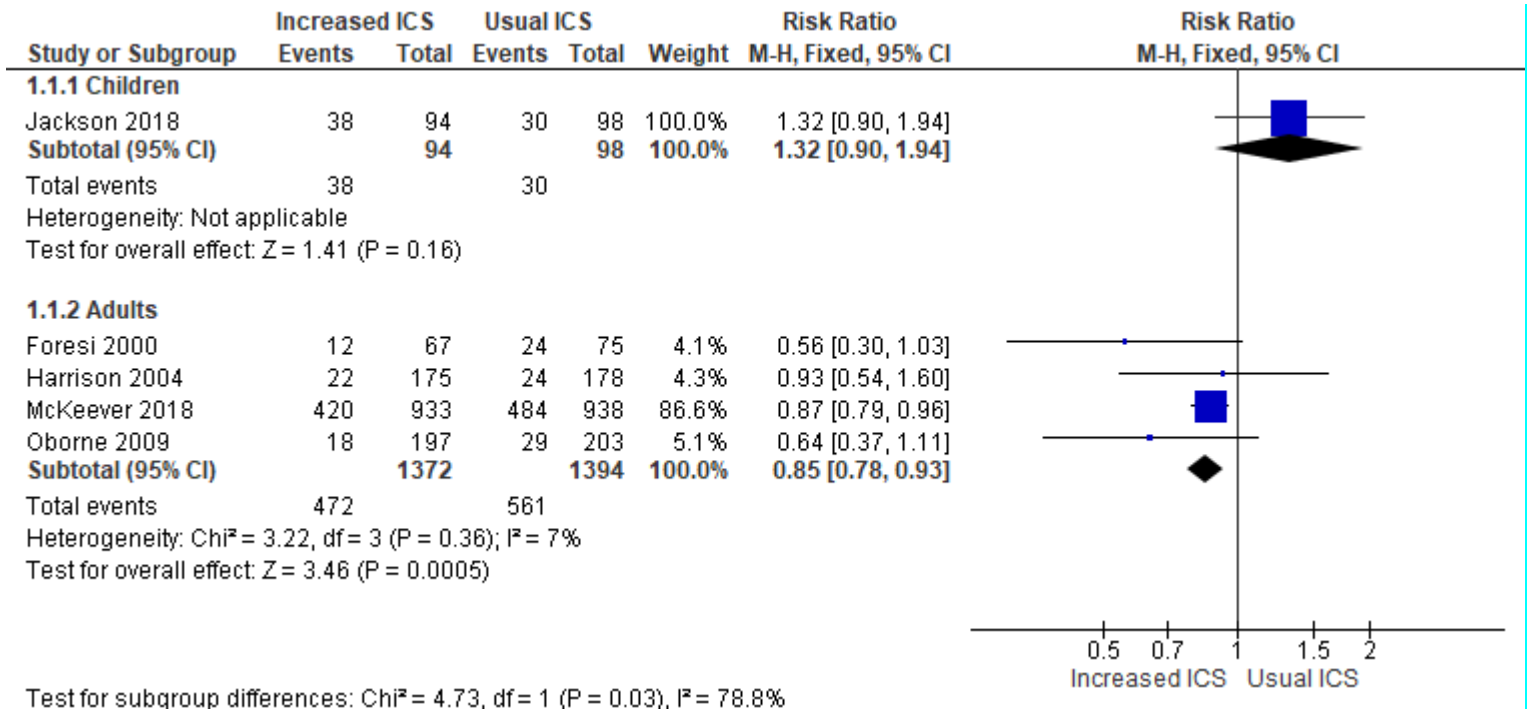
Overall bias and Directness

Risk of bias judgement

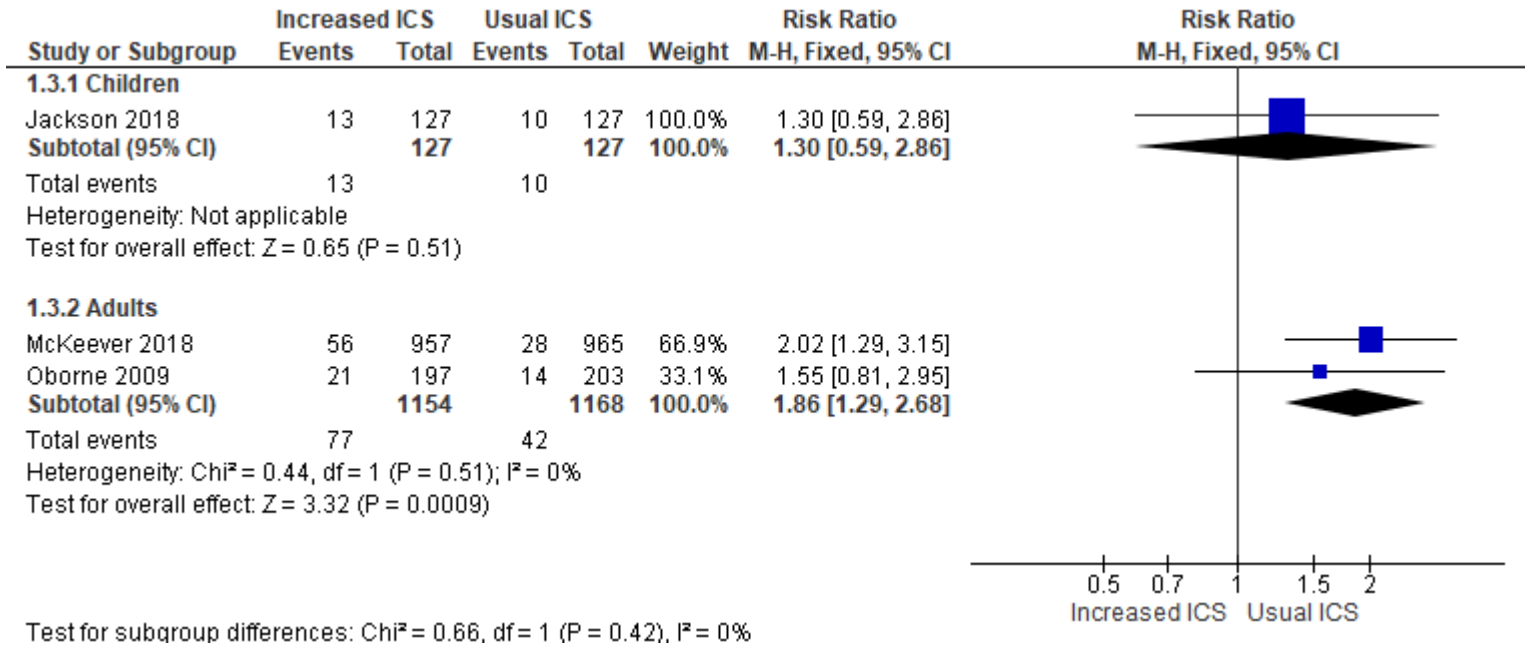
Low
Overall Directness
Indirectly applicable
(Involves a PAAP but is an adult study)

Appendix F – Forest plots

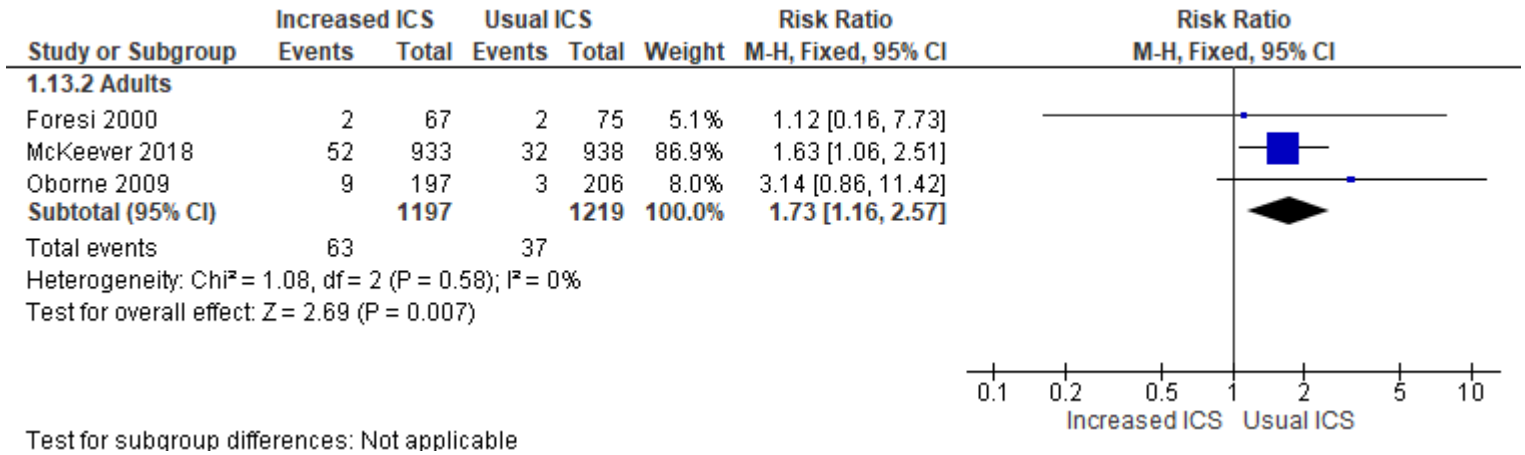
Subsequent asthma exacerbations for children and adults: Number of participants experiencing at least 1 severe asthma exacerbation during the study period (values greater than 1 favour usual ICS dose)



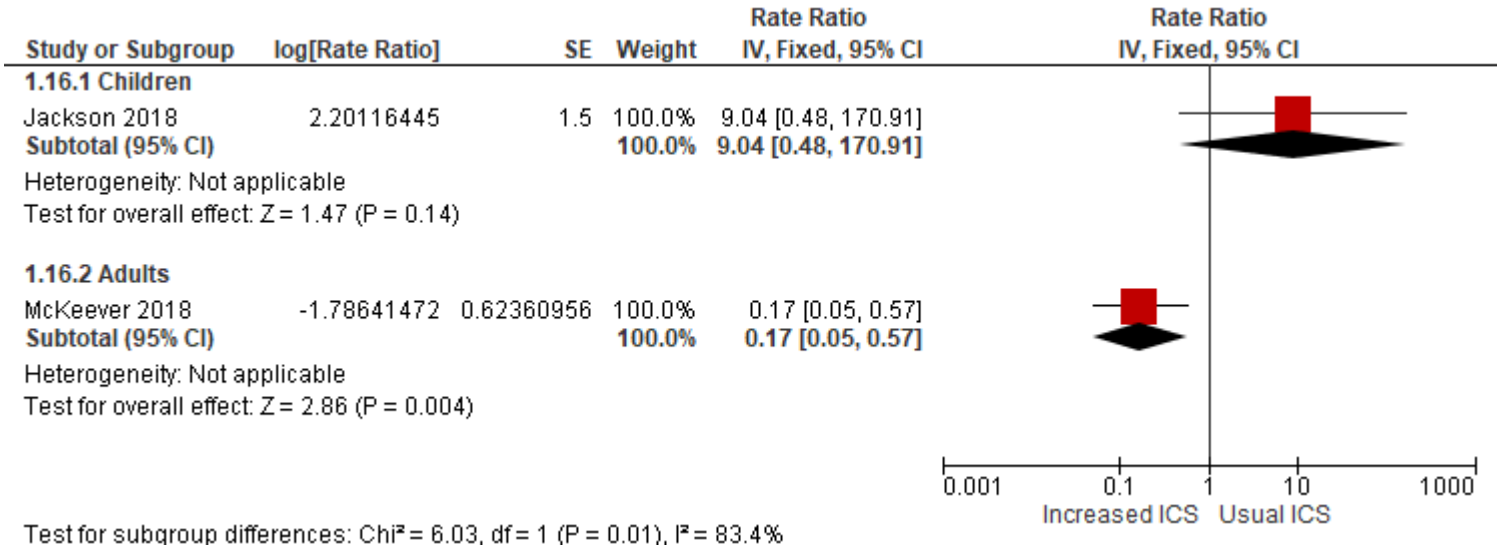
Treatment failure for children and adults: Participants who withdrew consent, had poor adherence and withdrew due to lack of efficacy (values greater than 1 favour usual ICS dose)



Adverse events for children and adults: Number of participants who experienced an adverse event (values greater than 1 favour usual ICS dose)



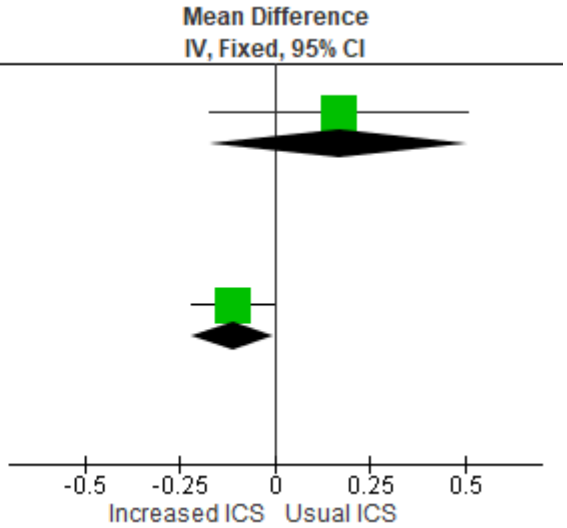
Adverse events for children and adults: Relative incidence rate of hospital admissions (incidents per year) (values greater than 1 favour usual ICS dose)



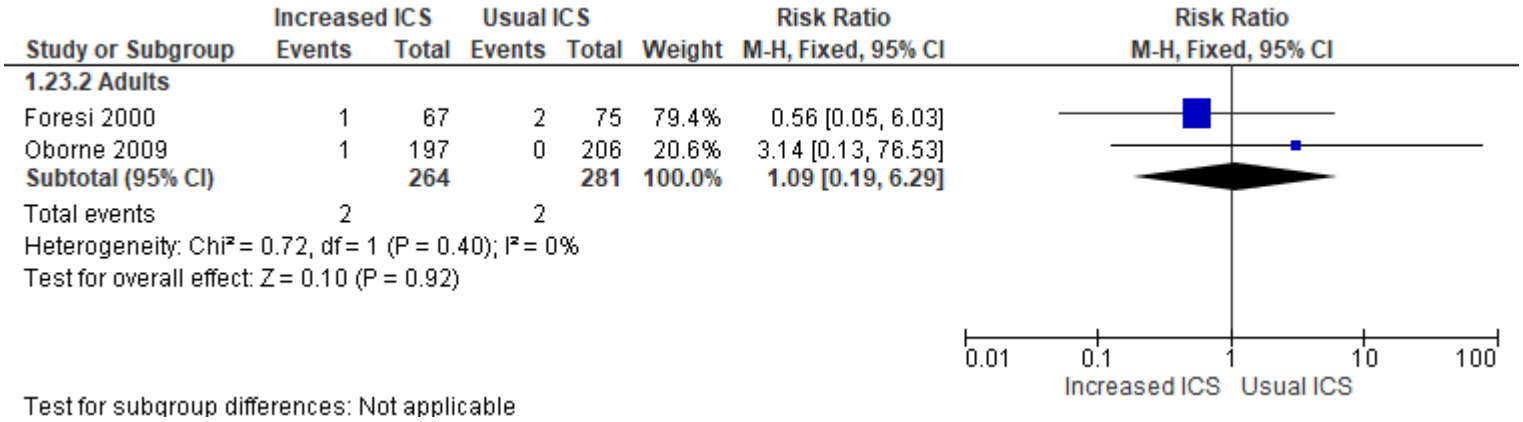
Adverse events for children and adults: Relative incidence rate of emergency department visits, urgent care visits, or unscheduled health care consultations per year (incidents per year) (values greater than 1 favour usual ICS dose)

Study or Subgroup	Increased ICS Mean	SD	Total	Usual ICS Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.18.1 Children								
Jackson 2018	0.64	1.3356	94	0.47	1.0354	98	100.0%	0.17 [-0.17, 0.51]
Subtotal (95% CI)			**94**			**98**	**100.0%**	**0.17 [-0.17, 0.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.98 (P = 0.33)								
1.18.2 Adults								
McKeever 2018	0.73	1.19	933	0.84	1.23	938	100.0%	-0.11 [-0.22, -0.00]
Subtotal (95% CI)			**933**			**938**	**100.0%**	**-0.11 [-0.22, -0.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.97 (P = 0.05)								

Test for subgroup differences: Chi² = 2.37, df = 1 (P = 0.12), I² = 57.8%



Adverse events for adults: Number of participants who experienced pharyngitis and/or laryngitis (values greater than 1 favour usual ICS dose)



Appendix G – GRADE tables

Usual ICS dose vs increased ICS dose

Outcomes that favoured the usual ICS dose

These outcomes only have adult data.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk per 1000: Usual ICS	Absolute risk per 1000: Increased ICS (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Adults: Adverse events: Number of participants who experienced an adverse event (values greater than 1 favour usual ICS dose) MID: 0.8 to 1.25										
3 (Foresi 2000, McKeever 2018, Oborne 2009)	Parallel RCTs	2866	RR 1.73 (1.16, 2.57)	30	53 (35, 78)	Very serious[1,2]	Very serious[3-5]	Not serious	Serious[6]	Very low
Adults: Treatment failure: participants who withdrew consent, had poor adherence or withdrew due to lack of efficacy (values greater than 1 favour usual ICS dose) MID 0.8 to 1.25										
2 (McKeever 2018, Oborne 2009)	Parallel RCTs	3320	RR 1.86 (1.29, 2.68)	36	67 (46, 96)	Very serious[2]	Very serious[4,5]	Not serious	Not serious	Very low

1. Foresi 2000 has a high risk of bias because the study does not say how many participants dropped out of each arm. There are no details regarding the method of randomisation. There are no details regarding the blinding of staff
2. McKeever 2018 has a high risk of bias because it was an unblinded study
3. Foresi 2000 is indirectly applicable because it is an adult study
4. McKeever 2018 is indirectly applicable because the interquartile range of the increased ICS dose group spans a mid-high to 2 times maximum high dose for adults. This is an adult study
5. Oborne 2009 is indirectly applicable because it is an adult study
6. 95% confidence interval crosses one end of a defined MID interval

Outcomes that favoured the increased ICS dose

These outcomes only have adult data.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk per 1000: Usual ICS	Absolute risk per 1000: Increased ICS (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Adults: Subsequent asthma exacerbations: Number of participants experiencing at least 1 severe asthma exacerbation during the study period (values greater than 1 favour usual ICS dose) MID 0.9 to 1.111										
4 (Foresi 2000, Harrison 2004, McKeever 2018, Oborne 2009)	Parallel RCTs	2766	RR 0.85 (0.78, 0.93)	402	342 (314, 374)	Very serious[1,2]	Very serious[3-6]	Not serious	Serious[7]	Very low
Adults, mean age 57.0 years (SD 15.0): Quality of life: Mini Asthma Quality of Life Questionnaire (scores range from 1 to 7, higher values indicating better quality of life) (values greater than 0 favour increased ICS dose) MID: 0.5										
1 (McKeever)	Parallel RCT	499	MD 0.30 (0.08, 0.52)	N/A	N/A	Very serious[2]	Very serious[5]	N/A	Serious[7]	Very low
Adults: Adverse events: Relative incidence rate of hospital admissions (incidents per year) (values greater than 1 favour usual ICS dose) MID: 0.9 to 1.111										
1 (McKeever 2018)	Parallel RCT	1871	RIR 0.17 (0.05, 0.57)	19	3 (1, 11)	Very serious[2]	Very serious[5]	N/A	Not serious	Very low
Adults: Lung function: Mean area under the curve of the peak expiratory flow (PEF) (values greater than 0 favour increased ICS dose) MID: 0.5										
1 (McKeever 2018)	Parallel RCT	529	MD 36.00 (10.23, 61.77)	N/A	N/A	Very serious[2]	Very serious[5]	N/A	Not serious	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk per 1000: Usual ICS	Absolute risk per 1000: Increased ICS (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. Foresi 2000 has a high risk of bias because the study does not say how many participants dropped out of each arm. There are no details regarding the method of randomisation. There are no details regarding the blinding of staff
2. McKeever 2018 has a high risk of bias because it was an unblinded study
3. Foresi 2000 is indirectly applicable because it is an adult study
4. Harrison 2004 is indirectly applicable because the increased dose was 2 times higher than the upper limit of maximum for adults. This is an adult study
5. McKeever 2018 is indirectly applicable because the interquartile range of the increased ICS dose group spans a mid-high to 2 times maximum high dose for adults. This is an adult study
6. Oborne 2009 is indirectly applicable because it is an adult study
7. 95% confidence interval crosses one end of a defined MID interval

Outcomes that showed no difference between groups

Outcomes for children are given first, followed by outcomes for adults.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk per 1000: Usual ICS	Absolute risk per 1000: Increased ICS (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Children: Subsequent asthma exacerbations: Number of participants experiencing at least 1 severe asthma exacerbation during the study period (values greater than 1 favour usual ICS dose) MID 0.9 to 1.111										
1 (Jackson 2018)	Parallel RCT	192	RR 1.32 (0.90, 1.94)	306	404 (276, 594)	Not serious	Serious[1]	N/A	Very serious[2]	Very low
Children: Treatment failure: participants who withdrew consent, had poor adherence and withdrew due to lack of efficacy (values greater than 1 favour usual ICS dose) MID 0.8 to 1.25										
1 (Jackson 2018)	Parallel RCT	254	RR 1.30 (0.59, 2.86)	79	102 (46, 225)	Not serious	Serious[1]	N/A	Very serious[2]	Very low

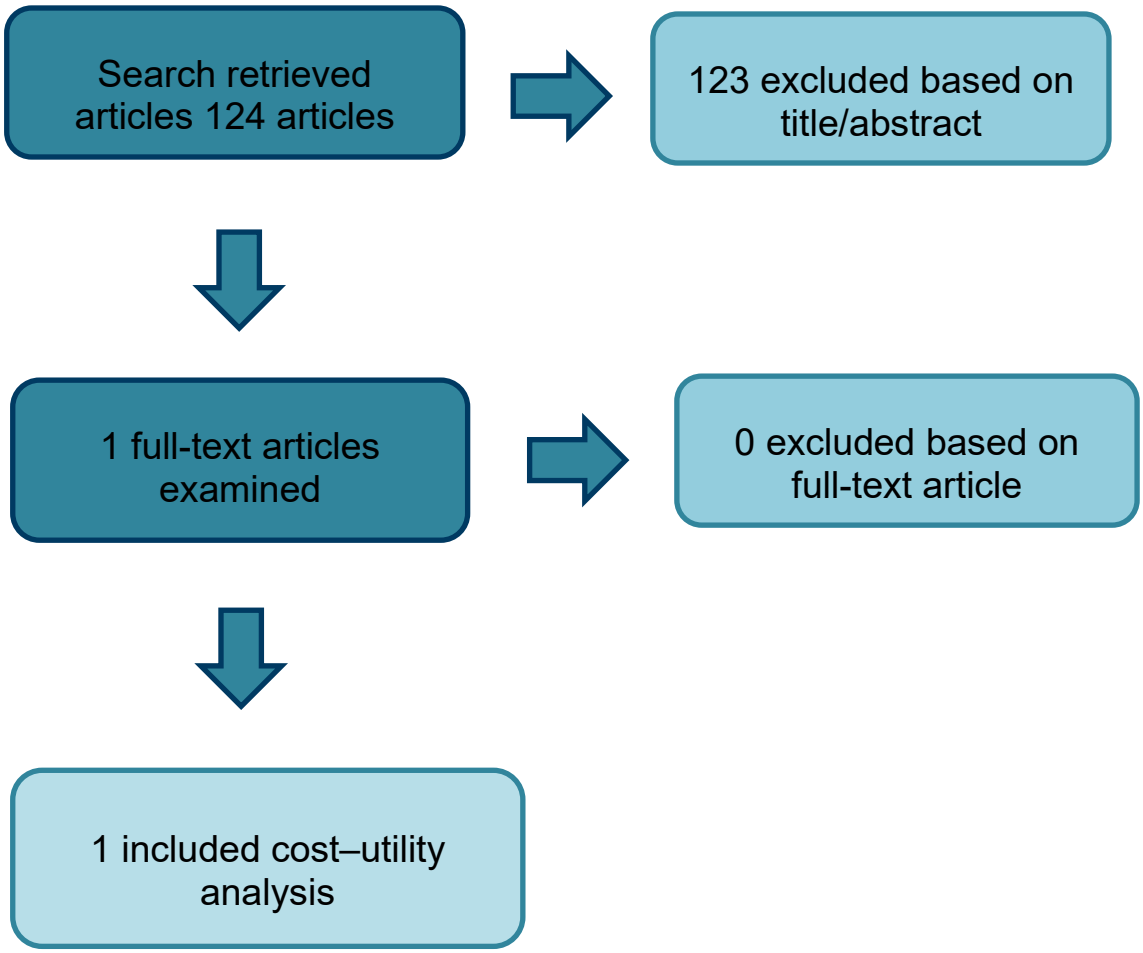
No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk per 1000: Usual ICS	Absolute risk per 1000: Increased ICS (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Children: Reliever medication use: Number of salbutamol inhalations per day from 7 days before to 14 days after the onset of yellow-zone alerts (values above 0 favour usual ICS dose) MID: 0.5										
1 (Jackson 2018)	Parallel RCT	192	MD 2.00 (-1.91, 5.91)	N/A	N/A	Not serious	Serious[1]	N/A	Serious[3]	Low
Children: Lung function: The percentage of days with Peak Expiratory Flows (PEFs) <80% of their reference value during the exacerbation period (yellow time zone) (values greater than 0 favour increased ICS dose) MID: 0.5										
1 (Jackson 2018)	Parallel RCT	192	MD -3.00 (-13.26, 7.26)	N/A	N/A	Not serious	Serious[1]	N/A	Very serious[2]	Very low
Children: Adverse events: Relative incidence rate of hospital admissions (incidents per year) (values greater than 1 favour usual ICS dose) MID: 0.5										
1 (Jackson 2018)	Parallel RCT	192	RIR 9.04 (0.48, 170.91)	N/A	N/A	Not serious	Serious[1]	N/A	Serious[3]	Low
Children: Adverse events: Relative incidence rate of emergency department visits, urgent care visits, or unscheduled health care consultations per year (values greater than 1 favour usual ICS dose) MID: 0.5										
1 (Jackson 2018)	Parallel RCT	192	RIR 0.17 (-0.17, 0.51)	N/A	N/A	Not serious	Serious[1]	N/A	Serious[3]	Low
Children: Adverse events: Relative rate of linear growth: centimetres per year (values greater than 1 favour increased ICS dose) MID: 0.5										
1 (Jackson 2018)	Parallel RCTs	192	MD -0.22 (-0.46, 0.02)	N/A	N/A	Not serious	Serious[1]	N/A	Serious[3]	Low
Adults: Lung function: Maximum fall in Peak Expiratory Flow (PEF) recorded at any time during the study, litres per minute (values greater than 0 favour usual ICS dose) MID: 18.79 L/min										
1 (Harrison 2004)	Parallel RCT	353	MD -10.00 (-20.90, 0.90)	N/A	N/A	Not serious	Very serious[4]	N/A	Serious[3]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk per 1000: Usual ICS	Absolute risk per 1000: Increased ICS (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Adults: Adverse events: Number of participants who experienced a serious adverse event (values greater than 1 favour usual ICS dose) MID: 0.8 to 1.25										
1 (McKeever 2018)	Parallel RCT	1871	RR 0.50 (0.25, 1.03)	23	12 (6, 24)	Very serious[5]	Very serious[6]	N/A	Serious[3]	Very low
Adults: Adverse events: Mortality (values greater than favour) MID: committee agreed no MID – no downgrading for imprecision										
1 (McKeever 2018)	Parallel RCT	1871	RR 3.02 (0.12, 73.94)	N/A[12]	N/A[12]	Very serious[5]	Very serious[6]	N/A	N/A	Very low
Adults: Adverse events: Relative incidence rate of emergency department visits, urgent care visits, or unscheduled health care consultations per year (values greater than 1 favour usual ICS dose) MID: 0.5										
1 (McKeever 2018)	Parallel RCT	1871	MD -0.11 (-0.22, 0.00)	N/A	N/A	Very serious[5]	Very serious[6]	N/A	Serious[3]	Very low
Adults: Adverse events: Number of participants who experienced pharyngitis and/or laryngitis (values greater than 1 favour usual ICS dose) MID: 0.8 to 1.25										
2 (Foresi 2000, Oborne 2009)	Parallel RCTs	545	RR 1.09 (0.19, 6.29)	7	8 (1, 45)	Very serious[7]	Very serious[8,9]	Not serious	Very serious[2]	Very low
Adults: Adverse events: Number of participants who experienced an upper respiratory tract infection (values greater than 1 favour usual ICS dose) MID: 0.8 to 1.25										
1 (Oborne 2009)	Parallel RCT	403	RR 3.14 (0.13, 76.53)	N/A	N/A	Not serious	Very serious[9]	N/A	Very serious[2]	Very low
Adults: Adverse events: Number of participants who experienced a lower respiratory tract infection (including pneumonia) (values greater than 1 favour usual ICS dose) MID: 0.8 to 1.25										
1 (McKeever 2018)	Parallel RCT	1871	RR 0.84 (0.26, 2.74)	6	5 (2, 18)	Very serious[5]	Very serious[6]	N/A	Very serious[2]	Very low
Adults: Adverse events: Number of participants who experienced sinusitis (values greater than 1 favour usual ICS dose) MID: 0.8 to 1.25										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk per 1000: Usual ICS	Absolute risk per 1000: Increased ICS (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Oborne 2009)	Parallel RCT	403	RR 0.35 (0.01, 8.50)	5	2 (1, 41)	Not serious	Very serious[9]	N/A	Very serious[2]	Very low

1. Jackson 2018 is partially applicable because the increased ICS dose was 2.2 times higher than the upper limit of maximum for children (NICE's advisory on ICS doses)
2. 95% confidence interval crosses both ends of a defined MID interval
3. 95% confidence interval crosses one end of a defined MID interval
4. Harrison 2004 is indirectly applicable because the increased dose was 2 times higher than the upper limit of maximum for adults. This is an adult study
5. McKeever 2018 has a high risk of bias because it was an unblinded study
6. McKeever 2018 is indirectly applicable because the interquartile range of the increased ICS dose group spans a mid-high to 2 times maximum high dose for adults. This is an adult study
7. Foresi 2000 has a high risk of bias because the study does not say how many participants dropped out of each arm. There are no details regarding the method of randomisation. There are no details regarding the blinding of staff
8. Foresi 2000 is indirectly applicable because it is an adult study
9. Oborne 2009 is indirectly applicable because it is an adult study

Appendix H – Economic evidence study selection



Appendix I – Economic evidence tables

Bibliographic reference	Study type	Study quality	Setting	Intervention	Comparator	Number of participants	Participant characteristics	Methods of analysis	Results	Limitations	Additional comments
McKeever T, Mortimer K, Bradshaw L, Haydock R, Pavord I, Higgins B, Walker S, Wilson A, Price D, Thomas M, Devereux G. Temporarily quadrupling the dose of inhaled steroid to prevent asthma exacerbations: FAST. Health Technology Assessment. 2018.	CUA alongside RCT	Partially applicable Potentially serious limitations	UK Primary care (potential participants identified from GP databases) and secondary care (patients attending respiratory outpatient appointments)	Self-management plan indicating quadrupling of normal ICS dose when poorly managed	Self-management plan without ICS modification	1,871	Age ≥16 years (mean 57) Asthma treated with ICS [i.e. steps 2–4 of BTS/SIGN) guidelines] 1 one or more exacerbations in the last 12 months requiring treatment with systemic corticosteroids	ICS micro-costed using diary cards Healthcare resource-use collected by questionnaire at 6 mo and 12 mo ± 2 mo Unit costs from PSSRU Costs of Health and Social Care (2015) and NHS Reference Costs (2014/15) QALYs from EQ-5D-3L area under the curve from measurement at baseline, 6- and 12-mo. Missing data (costs and QALYs) imputed (c30% of participants) Uncertainty explored using bootstrapping with replacement (5,000 replicates)	Costs (dose escalation -v-usual care): ICS: £42 -v- £17 ($p < 0.001$). Respiratory-related resource-use: £413 -v- £472 Total £415 -v- £431 (difference -£24 [-£122 to £71]). QALYs (dose escalation -v- usual care): 0.76 -v- 0.74 (difference 0.02 [-0.0 to 0.04; $p = 0.207$]). ICER: dose escalation dominates PSA: 94% chance dose-escalation is cost effective if QALYs are valued at £20K each (86% in complete cases only)	1-year time horizon (where mortality is an issue) Significant (c30%) missing data	NIHR RCT

Appendix J – Health economic model

Original health economic modelling was not undertaken for this review.

Appendix K – Excluded studies

Effectiveness studies

Study	Reason for exclusion
(2018) Severe exacerbations and inhaled corticosteroid load with as-needed budesonide/formoterol vs maintenance budesonide in mild asthma. American journal of respiratory and critical care medicine conference American thoracic society international conference ats 2018 united states197(meetingabstracts)	- Conference abstract
(2018) COST-CONSEQUENCE ANALYSIS OF FLUTICASONE FUROATE/VILANTEROL FOR ASTHMA MANAGEMENT IN SPAIN: AN ANALYSIS BASED ON THE SALFORD LUNG STUDY IN ASTHMA. Value in health 21: S410	- Conference abstract
Adachi, M; Kohno, Y; Minoguchi, K (2001) Step-down and step-up therapy in moderate persistent asthma. International archives of allergy and immunology 124(13): 414-6	- Data not reported in an extractable format
Adams, N; Bestall, J; Jones, PW (2001) Budesonide at different doses for chronic asthma. Cochrane database of systematic reviews (online): cd003271	- Systematic review used as source of primary studies
Adams, N; Bestall, JM; Jones, PW (2002) Inhaled fluticasone at different doses for chronic asthma. Cochrane database of systematic reviews (online): cd003534	- Systematic review used as source of primary studies
Adams, NP; Bestall, JC; Jones, P (2000) Budesonide at different doses for chronic asthma. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Adams, NP; Bestall, JC; Jones, P (1999) Beclomethasone at different doses for chronic asthma. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Adams, NP, Bestall, JC, Jones, P et al. (2008) Fluticasone at different doses for chronic	- Systematic review used as source of primary studies

Study	Reason for exclusion
asthma in adults and children. Cochrane Database of Systematic Reviews	
Adams, NP, Bestall, JC, Malouf, R et al. (2005) Beclomethasone versus placebo for chronic asthma. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Amar, Niran J, Shekar, Tulin, Varnell, Tracey A et al. (2017) Mometasone furoate (MF) improves lung function in pediatric asthma: A double-blind, randomized controlled dose-ranging trial of MF metered-dose inhaler. Pediatric pulmonology 52(3): 310-318	- Study is on mometasone furoate for children 5 to 11 years of age. It is not licensed for this use in the UK. Its safety and efficacy in children under 12 years of age has not yet been established.
Anonymous. (2005) Minimum maintenance dose required in asthma. Pharmaceutical Journal 274(7343): 382	- Narrative review
Axelsson, I, Naumburg, E, Prietsch, SOM et al. (2019) Inhaled corticosteroids in children with persistent asthma: effects of different drugs and delivery devices on growth. Cochrane Database of Systematic Reviews	- Did not compare one dose of ICS with a different dose of ICS
Ayres, J G and Campbell, L M (1996) A controlled assessment of an asthma self-management plan involving a budesonide dose regimen. OPTIONS Research Group. The European respiratory journal 9(5): 886-92	- Did not compare one dose of ICS with a different dose of ICS
Balter, M S; Adams, S G; Chapman, K R (2001) Inhaled beclomethasone dipropionate improves acoustic measures of voice in patients with asthma. Chest 120(6): 1829-34	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Bareille, P, Hardes, K, Robertson, J et al. (2013) Efficacy of a new selective steroid (GW870086) in asthma: an adaptive, randomised, controlled trial. Current drug therapy 8(2): 69-75	- An adjustable maintenance dosing regimen was used
Berger, WE, Milgrom, H, Chervinsky, P et al. (2006) Effects of treatment with mometasone furoate dry powder inhaler in children with persistent asthma. Annals of allergy, asthma & immunology 97(5): 672-680	- Study is on mometasone furoate for children 5 to 11 years of age. It is not licensed for this use in the UK. Its safety and efficacy in children under 12 years of age has not yet been established.

Study	Reason for exclusion
Bernstein, D I, Berkowitz, R B, Chervinsky, P et al. (1999) Dose-ranging study of a new steroid for asthma: mometasone furoate dry powder inhaler.. Respiratory medicine 93(9): 603-12	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Bjermer, L; Bengtsson, T; Jorup, C (2012) A comparison of the local and systemic effects of AZD3199, an inhaled ultra-long-acting beta2-adrenoceptor agonist (ULABA), with formoterol in patients with asthma. Journal of allergy and clinical immunology. 129(2suppl1): ab241	- Conference abstract
Busse, W (2001) The importance of efficacy and simplicity of dosing in establishing control of mild-to-moderate asthma. European respiratory review 11(78): 23-29	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Campbell, LM, Gooding, TN, Aitchison, WR et al. (1998) Initial loading (400 micrograms twice daily) versus static (400 micrograms nocte) dose budesonide for asthma management. PLAN Research Group. International journal of clinical practice 52(6): 361-8, 370	- Maximum duration of follow-up was less than 3 months
Castro-Rodriguez, Jose A; Rodrigo, Gustavo J; Rodriguez-Martinez, Carlos E (2015) Principal findings of systematic reviews for chronic treatment in childhood asthma. The Journal of asthma: official journal of the Association for the Care of Asthma 52(4): 407-16	- Systematic review used as source of primary studies
Cates, Christopher J and Karner, Charlotta (2013) Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. The Cochrane database of systematic reviews: cd007313	- Systematic review used as source of primary studies
Chanez, P; Karlstrom, R; Godard, P (2001) High or standard initial dose of budesonide to control mild-to-moderate asthma? The european respiratory journal 17(5): 856-862	- An adjustable maintenance dosing regimen was used
Chanez, P, Stallaert, R, Reznikova, E et al. (2010) Effect of salmeterol/fluticasone	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18

Study	Reason for exclusion
propionate combination on airway hyper-responsiveness in patients with well-controlled asthma. Respiratory medicine 104(8): 1101-9	years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Chapman, KR, Patel, P, D'Urzo, AD et al. (2005) Maintenance of asthma control by once-daily inhaled ciclesonide in adults with persistent asthma. Allergy 60(3): 330-337	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Chauhan, BF; Chartrand, C; Ducharme, FM (2013) Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Chauhan, Bhupendrasinh F, Chartrand, Caroline, Ni Chroinin, Muireann et al. (2015) Addition of long-acting beta2-agonists to inhaled corticosteroids for chronic asthma in children. The Cochrane database of systematic reviews: cd007949	- Systematic review used as source of primary studies
Chauhan, Bhupendrasinh F, Jeyaraman, Maya M, Singh Mann, Amrinder et al. (2017) Addition of anti-leukotriene agents to inhaled corticosteroids for adults and adolescents with persistent asthma. The Cochrane database of systematic reviews 3: cd010347	- Systematic review used as source of primary studies
Chipps, BE, Tashkin, DP, Uryniak, T et al. (2013) Effect of budesonide/formoterol pressurized metered-dose inhaler (BUD/FM pMDI) in African-American patients with moderate to severe asthma: responder analysis in patients with versus without fixed airflow obstruction (FAO). Journal of allergy and clinical immunology. 131(2suppl1): ab204	- Conference abstract
Chong, J, Haran, C, Chauhan, BF et al. (2015) Intermittent inhaled corticosteroid therapy versus placebo for persistent asthma in children and adults. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Collier, S, Barnes, N, Diar Bakerly, N et al. (2018) Contribution of asthma control test (ACT) total score ≥20 or improvement from baseline ≥3 to the composite primary effectiveness endpoint	- Conference abstract

Study	Reason for exclusion
in the salford lung study in asthma (SLS asthma). American journal of respiratory and critical care medicine 197(meetingabstracts)	
Corren J., Nelson H., Greos L.S. et al. (2001) Effective control of asthma with hydrofluoroalkane flunisolide delivered as an extrafine aerosol in asthma patients. Annals of Allergy, Asthma and Immunology 87(5): 405-411	- Flunisolide is not licensed for use in the UK
Dal Negro, R, Micheletto, C, Tognella, S et al. (2003) Assessment of inhaled BDP-dose dependency of exhaled nitric oxide and local and serum eosinophilic markers in steroids-naive nonatopic asthmatics. Allergy 58(10): 1018-22	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Edwards, S J, von Maltzahn, R, Naya, I P et al. (2010) Budesonide/formoterol for maintenance and reliever therapy of asthma: a meta analysis of randomised controlled trials. International journal of clinical practice 64(5): 619-27	- Systematic review used as source of primary studies
FitzGerald, J M, Becker, A, Sears, M R et al. (2004) Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. Thorax 59(7): 550-6	- Adult study that did not involve a randomised Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Garrett, J, Williams, S, Wong, C et al. (1998) Treatment of acute asthmatic exacerbations with an increased dose of inhaled steroid.. Archives of disease in childhood 79(1): 12-7	- ICS doses were not provided in this crossover study of 18 children. Wording in the methods section implies that beclomethasone and budesonide have similar efficacy and were therefore used interchangeably using the same doses. This crossover study had no washout period and was not conducted using the "two-treatment, two-period, two-group" methodology required in the Cochrane risk of bias tool
Ghosh, S, Kalmes, A, Mock, J et al. (2014) A Phase i assessment of safety and tolerability of RNS60, a novel therapeutic containing charge-stabilized nanostructures in asthma. Journal of allergy and clinical immunology. 133(2suppl1): ab4	- Conference abstract

Study	Reason for exclusion
Gilbert, Judith A (2018) Effect of increasing glucocorticoids on asthma exacerbations. The Lancet. Respiratory medicine 6(5): 328	- Narrative review
Goossens, Lucas M A, Riemersma, Roland A, Postma, Dirkje S et al. (2009) An economic evaluation of budesonide/formoterol for maintenance and reliever treatment in asthma in general practice. Advances in therapy 26(9): 872-85	- There has been a change in dose of other controller medications
Green, R H, Brightling, C E, McKenna, S et al. (2006) Comparison of asthma treatment given in addition to inhaled corticosteroids on airway inflammation and responsiveness.The European respiratory journal 27(6): 1144-51	- Maximum duration of follow-up was less than 3 months
Grzelewska-Rzymowska, I, Malolepszy, J, de Molina, M et al. (2003) Equivalent asthma control and systemic safety of inhaled budesonide delivered via HFA-134a or CFC propellant in a broad range of doses. Respiratory medicine 97suppld: 10-9	- Did not compare one dose of ICS with a different dose of ICS
Harrison, Lester I, Kurup, Sarala, Chen, Lin-Zhi et al. (2002) Pharmacokinetic comparison of beclomethasone dipropionate extrafine aerosol from two inhaler devices in children with asthma. European journal of clinical pharmacology 58(3): 191-5	- Maximum duration of follow-up was less than 3 months
Harrison, Lester I, Kurup, Sarala, Wagner, Craig et al. (2002) Pharmacokinetics of beclomethasone 17-monopropionate from a beclomethasone dipropionate extrafine aerosol in adults with asthma. European journal of clinical pharmacology 58(3): 197-201	- Maximum duration of follow-up was less than 3 months
Harrison, TW, Oborne, J, Newton, S et al. (2004) Doubling the dose of inhaled corticosteroid ineffective when asthma control is deteriorating. Australian journal of pharmacy 85(1011): 457	- Narrative review
Holt, S, Ryder-Lewis, S, Masoli, M et al. (2004) The use of novel fixed and adjustable dose symbicort self-management plans in asthma. American thoracic society 100th international	- Conference abstract

Study	Reason for exclusion
conference, May 21-26, 2004, orlando: b39posterc11	
Ind, P W, Dal Negro, R, Colman, N C et al. (2003) Addition of salmeterol to fluticasone propionate treatment in moderate-to-severe asthma. Respiratory medicine 97(5): 555-62	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Ismaila, Afisi S, Risebrough, Nancy, Li, Chunmei et al. (2014) COST-effectiveness of salmeterol/fluticasone propionate combination (Advair()) in uncontrolled asthma in Canada.. Respiratory medicine 108(9): 1292-302	- Narrative review
Jónasson, G; Carlsen, KH; Jonasson, C; Mowinckel, P; Low-dose inhaled budesonide once or twice daily for 27 months in children with mild asthma; Allergy; 2000; vol. 55 (no. 8); 740-748	- The children had no change in dose caused by a symptomatic change
Jonasson, G, Carlsen, K H, Sodal, A et al. (1999) Patient compliance in a clinical trial with inhaled budesonide in children with mild asthma. The European respiratory journal 14(1): 150-4	- The children had no change in dose caused by a symptomatic change
Jonasson, G; Carlsen, K-H; Mowinckel, P (2000) Asthma drug adherence in a long-term clinical trial. Archives of disease in childhood 83(4): 330-333	- The children had no change in dose caused by a symptomatic change
Jones, A, Fay, JK, Burr, ML et al. (2002) Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Jones, SL, Herbison, P, Cowan, JO et al. (2002) Exhaled NO and assessment of anti-inflammatory effects of inhaled steroid: dose-response relationship. The european respiratory journal 20(3): 601-608	- Maximum duration of follow-up was less than 3 months
Juniper, E F, Kline, P A, Vanzieleghem, M A et al. (1990) Long-term effects of budesonide on airway responsiveness and clinical asthma severity in inhaled steroid-dependent	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the

Study	Reason for exclusion
asthmatics. The European respiratory journal 3(10): 1122-7	participants' mean age and age 18 years, or a mean age of >30 years)
Katz, Y; Lebas, FX; Medley, HV; Robson, R; Fluticasone propionate 50 mug BID versus 100 mug BID in the treatment of children with persistent asthma; Clinical therapeutics; 1998; vol. 20 (no. 3); 424-437	- Children had not been taking ICS prior to the study (prior to increasing the ICS dose)
Kaiser, Sunitha V, Huynh, Tram, Bacharier, Leonard B et al. (2016) Preventing Exacerbations in Preschoolers With Recurrent Wheeze: A Meta-analysis. Pediatrics 137(6)	- Systematic review used as source of primary studies
Kannisto, S, Laatikainen, A, Taivainen, A et al. (2004) Serum dehydroepiandrosterone sulfate concentration as an indicator of adrenocortical suppression during inhaled steroid therapy in adult asthmatic patients. European journal of endocrinology 150(5): 687-690	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Kardos, P, Brüggenjürgen, B, Martin, A et al. (2001) Treatment of bronchial asthma using a new adjustable combination treatment plan: asthma Control Plan (ATACO). Pneumologie (stuttgart, germany) 55(5): 253-257	- Study not reported in English
Karpel, Jill P, Nayak, Anjuli, Lumry, William et al. (2007) Inhaled mometasone furoate reduces oral prednisone usage and improves lung function in severe persistent asthma. Respiratory medicine 101(3): 628-37	- There has been a change in dose of other controller medications
Kelly, HW, Van Natta, ML, Covar, RA et al. (2008) Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. Pediatrics 122(1): e53-61	- Did not compare one dose of ICS with a different dose of ICS
Kemp, JP, Berkowitz, RB, Miller, SD et al. (2000) Mometasone furoate administered once daily is as effective as twice-daily administration for treatment of mild-to-moderate persistent asthma. Journal of allergy and clinical immunology 106(3): 485-492	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)

Study	Reason for exclusion
Kerwin, EM, Gillespie, M, Song, S et al. (2017) Randomized, dose-ranging study of a fluticasone propionate multidose dry powder inhaler in adolescents and adults with uncontrolled asthma not previously treated with inhaled corticosteroids. Journal of asthma 54(1): 89-98	- Study uses RespiClick (Spiromax) to deliver fluticasone alone. This is an inhalation-driven, multidose dry powder inhaler. This was an experimental dose-ranging study. It appears to affect the dosing compared to a dry powder inhaler. RespiClick (Spiromax) appears to not be licensed to deliver fluticasone alone in the UK
Kew Kayleigh M, Karner Charlotta, Mindus Stephanie M, Ferrara Giovanni (2013) Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database of Systematic Reviews: Reviews issue12	- Duplicate reference
Kew, Kayleigh M, Karner, Charlotta, Mindus, Stephanie M et al. (2013) Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. The Cochrane database of systematic reviews: cd009019	- Did not compare one dose of ICS with a different dose of ICS
Kew, Kayleigh M, Quinn, Michael, Quon, Bradley S et al. (2016) Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. The Cochrane database of systematic reviews: cd007524	- Systematic review used as source of primary studies
Kharitonov, SA, Donnelly, LE, Montuschi, P et al. (2002) Dose-dependent onset and cessation of action of inhaled budesonide on exhaled nitric oxide and symptoms in mild asthma. Thorax 57(10): 889-896	- Maximum duration of follow-up was less than 3 months
Kupryś-Lipińska, I, Tworek, D, Vanderbist, F et al. (2013) Efficacy and safety of a 12-week therapy with a new formulation of fluticasone propionate at doses of 125 and 250 µg administered through a new generation cyclohaler twice daily, in comparison to fluticasone propionate 500 µg dry powder inhaler twice daily in patients with moderate asthma. Pneumonologia i alergologia polska 81(6): 527-536	- Fluticasone is administered using cyclohaler, which is not a preparation in the BNF

Study	Reason for exclusion
Langdon, C G, Adler, M, Mehra, S et al. (2005) Once-daily ciclesonide 80 or 320 microg for 12 weeks is safe and effective in patients with persistent asthma. Respiratory medicine 99(10): 1275-85	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Leather, D, Vestbo, J, Bakerly, ND et al. (2017) Late Breaking Abstract-Effectiveness of Fluticasone furoate/vilanterol (FF/VI) compared to usual care (UC) in patients with asthma: the Salford Lung Study (SLS). European respiratory journal 50	- Conference abstract
Lipworth, B J (1999) Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Archives of internal medicine 159(9): 941-55	- Systematic review used as source of primary studies
Lipworth, Brian J, Short, Philip M, Williamson, Peter A et al. (2012) A randomized primary care trial of steroid titration against mannitol in persistent asthma: STAMINA trial. Chest 141(3): 607-615	- An adjustable maintenance dosing regimen was used
Loymans, Rik J B, Gemperli, Armin, Cohen, Judith et al. (2014) Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: network meta-analysis. BMJ (Clinical research ed.) 348: g3009	- Systematic review used as source of primary studies
Lumry WR, Conway MM, LaForce CF et al. (2006) Fluticasone propionate hydrofluoroalkane inhalation aerosol in patients receiving inhaled corticosteroids. Ann Allergy Asthma Immunol. Jan;96(1):51-9	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Manning, P; Gibson, P G; Lasserson, T J (2008) Ciclesonide versus placebo for chronic asthma in adults and children. The Cochrane database of systematic reviews: cd006217	- Systematic review used as source of primary studies
Marogna, M, Braidi, C, Bruno, ME et al. (2013) The contribution of sublingual immunotherapy to the achievement of control in birch-related mild persistent asthma: a real-life randomised trial. Allergologia ET immunopathologia 41(4): 216-224	- Non-randomised observational study

Study	Reason for exclusion
Marogna, M, Braidi, C, Marco Emanuele, B et al. (2012) Sublingual immunotherapy and control of mild persistent asthma due to birch pollen: a real-life randomised trial. Allergy: european journal of allergy and clinical immunology. 67: 527	- Conference abstract
Maselli, DJ and Peters, JI (2018) Quadrupling inhaled glucocorticoid dose for deteriorating asthma control reduced severe exacerbations. Annals of internal medicine 168(12): JC65	- Narrative review
Masoli, M, Weatherall, M, Holt, S et al. (2004) Systematic review of the dose-response relation of inhaled fluticasone propionate. Archives of disease in childhood 89(10): 902-7	- Systematic review used as source of primary studies
Mckeever, T, Mortimer, K, Duley, L et al. (2017) Late Breaking Abstract-Can a self-management plan, which includes a four-fold increase in inhaled corticosteroid dose, reduce severe asthma exacerbations: a randomised, pragmatic trial. European respiratory journal 50	- Conference abstract
McKeever, Tricia, Mortimer, Kevin, Bradshaw, Lucy et al. (2018) Temporarily quadrupling the dose of inhaled steroid to prevent asthma exacerbations: FAST. Health technology assessment (Winchester, England) 22(70): 1-82	- A more detailed NIHR report of an already included study
Meltzer, EO, Baena-Cagnani, CE, Chervinsky, P et al. (2007) Once-daily mometasone furoate administered by dry powder inhaler for the treatment of children with persistent asthma. Pediatric asthma, allergy & immunology 20(2): 67-81	- Study is on mometasone furoate for children 4 to 11 years of age. It is not licensed for this use in the UK. Its safety and efficacy in children under 12 years of age has not yet been established.
Milanowski, J; Qualtrough, J; Perrin, V L (1999) Inhaled beclomethasone (BDP) with non-CFC propellant (HFA 134a) is equivalent to BDP-CFC for the treatment of asthma. Respiratory medicine 93(4): 245-51	- Non-randomised observational study
Millard, MW, Johnson, PT, McEwen, M et al. (2003) A randomized controlled trial using the school for anti-inflammatory therapy in asthma. Journal of asthma 40(7): 769-776	- Did not compare one dose of ICS with a different dose of ICS

Study	Reason for exclusion
Miller, SD, Orevillo, C, Nyberg, J et al. (2017) Efficacy and safety of budesonide delivered by metered dose inhaler (MDI) using a novel co-suspension™ delivery technology in adults with mild-to-moderate persistent asthma-a phase IIb dose-ranging study. American journal of respiratory and critical care medicine 195	- Conference abstract
Miraglia del Giudice, Michele, Piacentini, Giorgio L, Capasso, Michele et al. (2007) Formoterol, montelukast, and budesonide in asthmatic children: effect on lung function and exhaled nitric oxide. Respiratory medicine 101(8): 1809-13	- Maximum duration of follow-up was less than 3 months
Murphy, K, Berger, W, Engel, M et al. (2015) Tiotropium Respimat: control in symptomatic asthma. Journal of general internal medicine. 30: 77	- Conference abstract
Murphy, VE; Powell, H; Gibson, P (2015) Exacerbations following step down and step up inhaled corticosteroid therapy in the managing asthma in pregnancy (MAP) study. American journal of respiratory and critical care medicine 191	- Conference abstract
Murphy, VE; Powell, H; Gibson, PG (2015) Exacerbations of asthma following changes in inhaled corticosteroid (ICS) and long acting beta agonist (LABA) therapy in the managing asthma in pregnancy (MAP) study. Journal of paediatrics and child health 51: 64	- Conference abstract
Nair, A, Vaidyanathan, S, Clearie, K et al. (2010) Steroid sparing effects of intranasal corticosteroids in asthma and allergic rhinitis. Allergy 65(3): 359-67	- Maximum duration of follow-up was less than 3 months
Nathan, RA, Yancey, SW, Waitkus-Edwards, K et al. (2005) Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. Chest 128(4): 1910-1920	- Did not compare one dose of ICS with a different dose of ICS
Nolte, H, White, M, Weinstein, SF et al. (2012) Evaluation of diary data on asthma control factors managed with combined mometasone	- Conference abstract

Study	Reason for exclusion
furoate and formoterol fumarate in patients with severe asthma. Respirology (carlton, vic.) 17: 10	
Nolte, H, White, M, Weinstein, SF et al. (2012) Evaluation of diary data on asthma control factors managed with combined mometasone furoate and formoterol fumarate in patientswith severe asthma. Annals of allergy, asthma and immunology 109: A55	- Conference abstract
O'Byrne, P M, Barnes, P J, Rodriguez-Roisin, R et al. (2001) Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. American journal of respiratory and critical care medicine 164(8pt1): 1392-7	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Oliver, AJ; Covar, RA; Goldfrad, CH; Klein, RM; Pedersen, SE; Sorkness, CA; Tomkins, SA; Villaran, C; Grigg, J; Randomized Trial of Once-Daily Fluticasone Furoate in Children with Inadequately Controlled Asthma; Journal of pediatrics; 2016; vol. 178; 246-253.e2	- Children had not previously been taking ICS before the increase in dose of ICS.
Pedersen, SE, Prasad, N, Goehring, U-M et al. (2017) Control of moderate-to-severe asthma with randomized ciclesonide doses of 160, 320 and 640 mug/day. Journal of asthma and allergy 10: 35-46	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Phillips, K, Oborne, J, Harrison, T W et al. (2004) Use of sequential quadrupling dose regimens to study efficacy of inhaled corticosteroids in asthma. Thorax 59(1): 21-5	- Maximum duration of follow-up was less than 3 months
Pike, KC, Akhbari, M, Kneale, D et al. (2018) Interventions for autumn exacerbations of asthma in children. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Powell, H and Gibson, PG (2004) High dose versus low dose inhaled corticosteroid as initial starting dose for asthma in adults and children. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Powell, H and Gibson, PG (2003) Inhaled corticosteroid doses in asthma: an evidence-	- Narrative review

Study	Reason for exclusion
based approach. Medical journal of Australia 178(5): 223-225	
Pruteanu, AI, Chauhan, BF, Zhang, L et al. (2014) Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth. Evidence-based child health 9(4): 931-1046	- Systematic review used as source of primary studies
Pruteanu, AI, Chauhan, BF, Zhang, L et al. (2014) Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Quon Bradley S, FitzGerald J. Mark, LemiÃ¨re Catherine, Shahidi Neal, Ducharme Francine M (2010) Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. Cochrane Database of Systematic Reviews: Reviews issue12	- Systematic review used as source of primary studies
Quon, Bradley S, Fitzgerald, J Mark, Lemiere, Catherine et al. (2010) Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. The Cochrane database of systematic reviews: cd007524	- Systematic review used as source of primary studies
Quon, BS, FitzGerald, JM, Lemiere, C et al. (2010) Increased vs stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. Chest 138(4)	- Conference abstract
Reddel, H K, Jenkins, C R, Marks, G B et al. (2000) Optimal asthma control, starting with high doses of inhaled budesonide. The European respiratory journal 16(2): 226-35	- Maximum duration of follow-up was less than 3 months
Reddel, H K, Jenkins, C, Quirce, S et al. (2011) Effect of different asthma treatments on risk of cold-related exacerbations. The European respiratory journal 38(3): 584-93	- Narrative review
Rees T.P., Lennox B., Timney A.P. et al. (1993) Comparison of increasing the dose of budesonide to 800 mug/day with a maintained	- Maximum duration of follow-up was less than 3 months

Study	Reason for exclusion
dose of 400 mug/day in mild-to-moderate asthmatic patients. European Journal of Clinical Research 4: 67-77	
Rice-McDonald, G, Bowler, S, Staines, G et al. (2005) Doubling daily inhaled corticosteroid dose is ineffective in mild to moderately severe attacks of asthma in adults. Internal medicine journal 35(12): 693-8	- Maximum duration of follow-up was less than 3 months
Riemersma, RA; Postma, D; van der Molen, T (2012) Budesonide/formoterol maintenance and reliever therapy in primary care asthma management: effects on bronchial hyperresponsiveness and asthma control. Primary care respiratory journal 21(1): 50-56	- Did not compare one dose of ICS with a different dose of ICS
Ruff, ME; Szefler, SJ; Meltzer, EO; Berger, WE; Efficacy and safety of extrafine beclomethasone dipropionate aerosol therapy in children with asthma: a twelve-week placebo-controlled trial; Pediatric asthma, allergy & immunology; 2003; vol. 16 (no. 1); 1-13	- Children were not prescribed ICS before they were given an increased dose
Sears, M R, Boulet, L-P, Laviolette, M et al. (2008) Budesonide/formoterol maintenance and reliever therapy: impact on airway inflammation in asthma. The European respiratory journal 31(5): 982-9	- Did not compare one dose of ICS with a different dose of ICS
Selroos, O, Lofroos, AB, Pietinalho, A et al. (2004) Asthma control and steroid doses 5 years after early or delayed introduction of inhaled corticosteroids in asthma: a real-life study. Respiratory medicine 98(3): 254-262	- Non-randomised observational study
Shepherd, J, Rogers, G, Anderson, R et al. (2008) Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over. Health technology assessment (Winchester, England) 12(19): iii-360	- Systematic review used as source of primary studies
Shrewsbury S, Pyke S, Britton M (2000) Meta-analysis of increased dose of inhaled steroid or	- Did not compare one dose of ICS with a different dose of ICS

Study	Reason for exclusion
addition of salmeterol in symptomatic asthma (MIASMA). BMJ 320: 1368-1373	
Simons, E and Wood, RA (2005) Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. Pediatrics 116(2): 564	- Narrative review
Skoner, D P, Szefler, S J, Welch, M et al. (2000) Longitudinal growth in infants and young children treated with budesonide inhalation suspension for persistent asthma. The Journal of allergy and clinical immunology 105(2pt1): 259-68	- Narrative review
Stelmach, I; Bobrowska-Korzeniowska, M; Majak, P; Stelmach, W; Kuna, P; The effect of montelukast and different doses of budesonide on IgE serum levels and clinical parameters in children with newly diagnosed asthma; Pulmonary pharmacology & therapeutics; 2005; vol. 18 (no. 5); 374-380	- Children were not prescribed ICS before there was an increase in ICS dose
Subbarao, P, Duong, M, Adelroth, E et al. (2006) Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma. Journal of allergy and clinical immunology 117(5): 1008-1013	- Maximum duration of follow-up was less than 3 months
Sumino, K, Bacharier, LB, Taylor, J et al. (2018) The real-world effectiveness of symptom-based, intermittent inhaled corticosteroid adjustment in african american children with asthma. American journal of respiratory and critical care medicine 197(meetingabstracts)	- Conference abstract
Sumino, Kaharu, Sugar, Elizabeth A, Irvin, Charles G et al. (2014) Variability of methacholine bronchoprovocation and the effect of inhaled corticosteroids in mild asthma. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology 112(4): 354-60e1	- Maximum duration of follow-up was less than 3 months
Svedsater, H, Jones, R, Bosanquet, N et al. (2018) Patient-reported outcomes with initiation of fluticasone furoate/vilanterol versus	- Did not compare one dose of ICS with a different dose of ICS

Study	Reason for exclusion
continuing usual care in the Asthma Salford Lung Study. Respiratory medicine 141: 198-206	
Takeyama, K, Kondo, M, Tagaya, E et al. (2013) Efficacy and tolerability of budesonide/formoterol maintenance and reliever therapy in Japanese patients with moderate to severe persistent asthma. American journal of respiratory and critical care medicine 187	- Conference abstract
Vastagh, E, Kuna, P, Calistruc, P et al. (2003) Efficacy and safety of inhaled budesonide delivered once or twice daily via HFA-134a in mild to moderate persistent asthma in adult patients. Comparison with budesonide CFC. Respiratory medicine 97suppld: S20-8	- Did not compare one dose of ICS with a different dose of ICS
Visser, MJ, Postma, DS, Brand, PL et al. (2002) Influence of different dosage schedules of inhaled fluticasone propionate on peripheral blood cytokine concentrations in childhood asthma. Clinical and experimental allergy 32(10): 1497-1503	- No outcomes of interest. Study only looks at cytokine levels
Visser, MJ, van der Veer, E, Postma, DS et al. (2004) Side-effects of fluticasone in asthmatic children: no effects after dose reduction. The european respiratory journal 24(3): 420-425	- An adjustable maintenance dosing regimen was used
Voorham, J, Roche, N, Benhaddi, H et al. (2018) Real-world effectiveness evaluation of budesonide/formoterol Spiromax for the management of asthma and chronic obstructive pulmonary disease in the UK. BMJ open 8(10)	- Non-randomised observational study
Wang K., Tian P., Fan Y. et al. (2015) Assessment of second-line treatments for patients with uncontrolled moderate asthma. International Journal of Clinical and Experimental Medicine 8(10): 19476-19480	- Did not compare one dose of ICS with a different dose of ICS
Wasserman, RL, Baker, JW, Kim, KT et al. (2006) Efficacy and safety of inhaled fluticasone propionate chlorofluorocarbon in 2- to 4-year-old patients with asthma: results of a double-blind, placebo-controlled study. Annals of allergy, asthma & immunology 96(6): 808-818	- Study is on fluticasone propionate for children 2 to 4 years of age. It is not licensed for children 4 years of age and younger in the UK

Study	Reason for exclusion
Wennergren, G, Nordvall, S L, Hedlin, G et al. (1996) Nebulized budesonide for the treatment of moderate to severe asthma in infants and toddlers. Acta paediatrica (Oslo, Norway: 1992) 85(2): 183-9	- An adjustable maintenance dosing regimen was used
Wolfe, J D, Selner, J C, Mendelson, L M et al. (1996) Effectiveness of fluticasone propionate in patients with moderate asthma: a dose-ranging study. Clinical therapeutics 18(4): 635-46	- Adult study that did not involve a Personalised Asthma Action Plan (Recruitment age >18 years, or >1 standard deviation between the participants' mean age and age 18 years, or a mean age of >30 years)
Wolthers, OD and Heuck, C (2004) Impact of Age and Administration Regimens on the Suppressive Effect of Inhaled Glucocorticoids on Eosinophil Markers in Children with Asthma. Pediatric asthma, allergy & immunology 17(1): 45-51	- Maximum duration of follow-up was less than 3 months
Woodcock, A, Vestbo, J, Bakerly, ND et al. (2017) Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial. Lancet (london, england) 390(10109): 2247-2255	- Did not compare one dose of ICS with a different dose of ICS
Woolcock, A, Lundback, B, Ringdal, N et al. (1996) Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. American journal of respiratory and critical care medicine 153(5): 1481-8	- There has been a change in dose of other controller medications
Yousef, E; Hossain, J; Mannnan, S (2011) Ineffectiveness of high-dose inhaled corticosteroids for control of pre-exacerbation asthma symptoms; Randomized controlled trial. Journal of allergy and clinical immunology 127(2): AB85	- Conference abstract
Yousef, Ejaz, Hossain, Jobayer, Mannan, Susan et al. (2012) Early intervention with high-dose inhaled corticosteroids for control of acute asthma exacerbations at home and improved outcomes: a randomized controlled trial. Allergy and asthma proceedings 33(6): 508-13	- Maximum duration of follow-up was less than 3 months
Zeiger, Robert S, Mauger, David, Bacharier, Leonard B et al. (2011) Daily or intermittent	- Did not compare one dose of ICS with a different dose of ICS

Study	Reason for exclusion
budesonide in preschool children with recurrent wheezing. The New England journal of medicine 365(21): 1990-2001	
Zhang Y., He J., Yuan Y. et al. (2019) Increased versus Stable Dose of Inhaled Corticosteroids for Asthma Exacerbations: A Systematic Review and Meta-analysis. Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology	- Systematic review used as source of primary studies
Zhang, L; Prietsch, SOM; Ducharme, FM (2014) Inhaled corticosteroids in children with persistent asthma: effects on growth. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Zietkowski, Z, Lukaszyk, M, Skiepko, R et al. (2015) Efficacy of ciclesonide in the treatment patients with asthma exacerbation. Allergy: european journal of allergy and clinical immunology. 70: 556	- Maximum duration of follow-up was less than 3 months
Zimmerman B.; Johnston P.; Zimmerman R.S. (1999) Blood eosinophils and serum ECP in childhood asthma: Response to increased doses of inhaled steroid in 'controlled' asthma. Canadian Journal of Allergy and Clinical Immunology 4(1): 16-24	- Maximum duration of follow-up was less than 3 months
ZuWallack, R L, Rosen, J P, Cohen, L et al. (1997) The effectiveness of once-daily dosing of inhaled flunisolide in maintaining asthma control. The Journal of allergy and clinical immunology 99(3): 278-85	- This was a step-down study: Participants began with well controlled asthma and the dose of ICS was reduced

Cost-effectiveness studies

No studies were excluded at full-text review.

Appendix L – Research recommendations – full details

Research recommendation

For children who have asthma that is managed in primary care, is there an advantage to increasing the ICS dose when asthma control has deteriorated compared to using the usual dose in a personalised asthma plan?

Why this is important

A self-initiated quadrupling of the dose of maintenance ICS when asthma worsens has been a common treatment to reduce the chances of exacerbations occurring. However, there is data of very low quality on this.

Rationale for research recommendation

Importance to children with asthma	The UK's asthma outcomes for children are 5 times worse than other European countries in terms of admissions and mortality. There is currently insufficient evidence to either support or refute the use of increasing ICS when asthma control deteriorates
Relevance to the NICE guidance	Increasing the dose of maintenance ICS when asthma worsens could reduce the chances of exacerbations occurring
Relevance to the NHS	The outcome may reduce the number of exacerbations experienced by children reducing emergency department visits and hospital admissions.
National priorities	Moderate
Current evidence base	1 child RCT that has very low-quality data (Jackson 2018). The new study should be different from this study in the following ways: • It should have a greater number of participants (the number of children required should be over 5000) • It should use an increased dose of ICS that does not exceed the licensed dose limit
Equality considerations	Some families are less structured in their use of healthcare and resources

Modified PICO table

Population	• Children and young people with a clinical diagnosis of asthma, using ICS preventer therapy, who are receiving supported self-management including a personalised action plan.

	• Setting – primary care (a pragmatic study) • Adherence monitoring if possible
Intervention	Self-initiated increase of the dose of ICS because of worsening asthma, as advised on their personalised action plan. If possible it would be good to have additional arms of the study with different doses of ICS to see if there is a dose-response effect. Ideally, there should be adherence monitoring. The personalised action plan should be on a smartphone app otherwise many children won't use it
Comparator	Keeping the usual maintenance dose of ICS as part of a personalised action plan at the onset of worsening asthma. Ideally, there should be adherence monitoring. The personalised action plan should be on a smartphone app
Outcomes	Critical outcome: subsequent asthma exacerbations where emergency treatment was sought Other outcomes: oral corticosteroids needed; treatment failure; mortality; quality of life; school days missed; parents' workdays missed; asthma control; hospital admissions; reliever/rescue medication use; lung function for children who are old enough; oxygen saturation; adverse events (including safety and growth). Ideally the study would include biomarkers to identify any subgroup(s) that are particularly responsive to an increased ICS dose
Study design	Randomised controlled trial
Timeframe	Long term
Additional information	The committee suggested that the CPRD GP database be used because the number of children required should be over 5000